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(54) Title: SUBSTITUTED OXOAZAHETEROCYCLYL COMPOUNDS

(57) Abstract: This invention is directed to oxoazaheterocyclyl compounds which inhibit Factor Xa, to oxoazaheterocyclyl compounds which inhibit both Factor Xa and Factor IIa, to pharmaceutical compositions comprising these compounds, to intermediates useful for preparing these compounds, to a method of directly inhibiting Factor Xa and to a method of simultaneously directly inhibiting Factor Xa and Factor IIa.

Description

SUBSTITUTED OXOAZAHETEROCYCLYL COMPOUNDS

5 FIELD OF THE INVENTION

This invention is directed to oxoazaheterocyclyl compounds which inhibit Factor

This invention is directed to oxoazaheterocyclyl compounds which inhibit Factor Xa, to pharmaceutical compositions comprising these compounds, to intermediates useful for preparing these compounds and to a method of inhibiting Factor Xa. This invention is also 10 directed to oxoazaheterocyclyl compounds which directly inhibit both Factor Xa and Factor IIa (thrombin), to pharmaceutical compositions comprising these compounds, to intermediates useful for preparing these compounds and to a method of simultaneously directly inhibiting both Factor Xa and Factor IIa (thrombin).

BACKGROUND OF THE INVENTION

15 Factor Xa and Factor Xa assembled in the prothrombinase complex (Factor Xa, Factor Va, calcium and phospholipid) activate prothrombin (Factor II) to generate thrombin (Factor IIa). Factor Xa is strategically located at the intersection of extrinsic and intrinsic pathways of the blood coagulation system. Thus, an inhibitor of Factor Xa inhibits the formation of thrombin and, therefore, is useful for preventing or treating disorders related to blood coagulation in 20 mammals.

Anticoagulant therapy is indicated for the treatment and prophylaxis of a variety of thrombotic conditions of both the venous and arterial vasculature. In the arterial system, abnormal thrombus formation is primarily associated with arteries of the coronary, cerebral and peripheral vasculature. The diseases associated with thrombotic occlusion of these vessels 25 principally include acute myocardial infarction (AMI), unstable angina, thromboembolism, acute vessel closure associated with thrombolytic therapy and percutaneous transluminal coronary angioplasty (PTCA), transient ischemic attacks, stroke, intermittent claudication and bypass grafting (CABG) of the coronary or peripheral arteries. Chronic anticoagulant therapy may also be beneficial in preventing the vessel luminal narrowing (restenosis) that often occurs following 30 PTCA and CABG, and in the maintenance of vascular access patency in long-term hemodialysis patients. With respect to the venous vasculature, pathologic thrombus formation frequently occurs in the veins of the lower extremities following abdominal, knee and hip 35 surgery (deep vein thrombosis, DVT). DVT further predisposes the patient to a higher risk of pulmonary thromboembolism. A systemic, disseminated intravascular coagulopathy (DIC) commonly occurs in both vascular systems during septic shock, certain viral infections and

cancer. This condition is characterized by a rapid consumption of coagulation factors and their plasma inhibitors resulting in the formation of life-threatening clots throughout the microvasculature of several organ systems.

In addition to their use in anticoagulant therapy, Factor Xa inhibitors are useful in the treatment or prevention of other diseases in which the generation of thrombin has been implicated as playing a physiologic role. For example, thrombin has been proposed to contribute to the morbidity and mortality of such chronic and degenerative diseases as arthritis, cancer, atherosclerosis and Alzheimer's disease by virtue of its ability to regulate many different cell types through specific cleavage and activation of a cell surface thrombin receptor, mitogenic effects, diverse cellular functions such as cell proliferation, for example, abnormal proliferation of vascular cells resulting in restenosis or angiogenesis, release of PDGF and DNA syntheses. Inhibition of Factor Xa will effectively block thrombin generation and therefore neutralize any physiologic effects of thrombin on various cell types.

The representative indications discussed above include some, but not all, of the possible clinical situations amenable to treatment with a Factor Xa inhibitor.

Oxoazaheterocycl Factor Xa inhibitors are disclosed in International Patent Application Numbers PCT/US98/07158, published Oct. 22, 1998; PCT/US98/07159, published Oct. 22, 1998; PCT/US98/07160, published Oct. 22, 1998; PCT/US98/07161, published Oct. 22, 1998; and PCT/US96/09290, published Dec. 19, 1996. Oxoazaheterocycl fibrinogen antagonists are disclosed in International Patent Application Number PCT/US92/09467, published May 13, 1993.

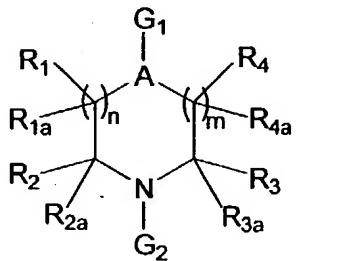
Vascular injury, caused by biochemical or physical perturbations, results in the activation of the coagulation system, culminating in the generation of thrombin. Thrombin promotes thrombus formation by catalyzing the transformation of fibrinogen to fibrin, by activating Coagulation Factor XIII, which stabilizes the thrombus, and by activating platelets. Thrombin promotes further thrombus growth by positive feedback to the coagulation cascade (activation of Coagulation Factors V and VIII), resulting in the explosive production of thrombin. Thrombin is present, and active, in the thrombi of patients with thrombotic vascular disease. Thrombin inhibition prevents the action of thrombin after thrombin has been activated from prothrombin. An inhibitor of thrombin inhibits cleavage of fibrinogen to fibrin, activation of Factor XIIIa, activation of platelets, and feedback of thrombin to the coagulation cascade to generate more thrombin. Consequently, inhibition of thrombin activity with a direct thrombin inhibitor would be useful for preventing or treating disorders related to blood coagulation in mammals.

The combined inhibitors of Factor Xa and Factor IIa described herein inhibit thrombin activity (via IIa inhibition) and thrombin production (via Factor Xa inhibition). Therefore, these

agents inhibit any thrombin that may be present and also inhibit the further production of thrombin. Other agents which have this dual activity include heparin and low molecular weight heparins (LMWHs), which have demonstrated efficacy in thrombotic diseases. However, heparin and LMWHs act indirectly through a cofactor, antithrombin-III (ATIII), to inhibit Xa and IIa. The heparin/ATIII complex is too large, however, to inhibit thrombus-bound Xa and IIa, thus limiting its efficacy. Direct inhibitors of Factor Xa and Factor IIa, as described herein, are capable of inhibiting soluble and thrombus-bound Xa and IIa, thus providing an important therapeutic advantage over currently available Xa/IIa inhibitors.

10 SUMMARY OF THE INVENTION

This invention is directed to a compound of formula I



or a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof

15 wherein

G₁ and G₂ are L₁-Cy₁ or L₂-Cy₂, provided that when R₁ and R_{1a} or R₄ and R_{4a} taken together form O or S, then G₁ is L₂-Cy₂ and G₂ is L₁-Cy₁, or when R₂ and R_{2a} or R₃ and R_{3a} taken together form O or S, then G₁ is L₁-Cy₁ and G₂ is L₂-Cy₂;

Cy₁ and Cy₂ are independently selected from optionally substituted aryl, optionally substituted

20 heteroaryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocycl, optionally substituted heterocyclenyl, optionally substituted fused arylcycloalkyl, optionally substituted fused arylcycloalkenyl, optionally substituted fused arylheterocycl, optionally substituted fused arylheterocyclenyl, optionally substituted fused heteroarylalkyl, optionally substituted fused heteroarylalkenyl, optionally substituted fused

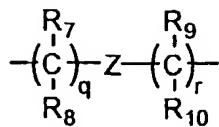
25 fused heteroarylalkyl and optionally substituted fused heteroarylalkenyl;

L₁ is absent, O, NR₅, -S(O)p-, -S(O)pNR₅-, -C(X)Y- or -L₃-Q-L₄-Q'-L₅-, -C(O)Y-C(X)Y-, -

C(X)YC(O)-,

-C(O)NR₅-S(O)p-, or -C(O)C(O)NR₅S(O)p-;

L₂ is absent or a group of formula



L_3 and L_5 are independently absent, optionally substituted alkylene, optionally substituted alkenylene or optionally substituted alkynylene;

L_4 is optionally substituted alkylene, optionally substituted alkenylene, or optionally substituted alkynylene;

5 S alkynylene;

Q and Q' are independently absent, O , S , NR_5 , $-\text{S}(\text{O})\text{p}-$, $-\text{S}(\text{O})\text{pNR}_5-$ or $-\text{C}(\text{X})\text{Y}-$;

A is CH or N ;

R_1 , R_{1a} , R_2 , R_{2a} , R_3 , R_{3a} , R_4 and R_{4a} are independently selected from hydrogen, carboxy, alkoxy carbonyl, $\text{Y}_1\text{Y}_2\text{NC(O)}-$, optionally substituted alkyl, optionally substituted aryl, optionally

10 substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl, or R_1 and R_{1a} , R_2 and R_{2a} , R_3 and R_{3a} , or R_4 and R_{4a} taken together form O or S ; or R_1 and R_2 together with the carbon atoms through which R_1 and R_2 are linked form a cycloalkyl group, cycloalkenyl group, heterocycl group, or heterocyclenyl group; or R_3 and R_4 together with the carbon atoms through which R_3 and R_4 are linked form a cycloalkyl group, cycloalkenyl group,

15 heterocycl group, or heterocyclenyl group; or R_{1a} and R_{2a} are absent and R_1 and R_2 together with the carbon atoms through which R_1 and R_2 are linked form an aryl or heteroaryl group; or R_{3a} and R_{4a} are absent and R_3 and R_4 together with the carbon atoms through which R_3 and R_4 are linked form an aryl or heteroaryl group; or one or more of the pairs R_1 and R_{1a} taken

20 together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; or R_2 and R_{2a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; or R_3 and R_{3a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; or R_4 and R_{4a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group;

25 m and n are independently 0, 1 or 2, provided that m and n are not both 0 and further provided that when R_1 and R_{1a} taken together form O or S , n is 1, and when R_4 and R_{4a} taken together form O or S , m is 1;

R_5 is hydrogen, optionally substituted alkyl, optionally substituted aralkyl, optionally substituted heteroaralkyl, $\text{R}_6\text{O}(\text{CH}_2)\text{v}-$, $\text{R}_6\text{O}_2\text{C}(\text{CH}_2)\text{x}-$, $\text{Y}_1\text{Y}_2\text{NC(O)}(\text{CH}_2)\text{x}-$, or $\text{Y}_1\text{Y}_2\text{N}(\text{CH}_2)\text{v}-$;

30 R_6 is hydrogen, optionally substituted alkyl, optionally substituted aralkyl or optionally substituted heteroaralkyl;

Y_1 and Y_2 are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, optionally substituted aryl, optionally substituted aralkyl or

optionally substituted heteroaralkyl, or Y_1 and Y_2 taken together with the N through which Y_1 and Y_2 are linked form a monocyclic heterocyclyl;

R_7 , R_8 , R_9 and R_{10} are independently selected from hydrogen, hydroxy, alkoxy, optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted aralkyl and optionally substituted heteroaralkyl, provided that only one of R_7 and R_8 or one of R_9 and R_{10} is hydroxy or alkoxy, and further provided when any of R_7 , R_8 , R_9 and R_{10} is hydroxy or alkoxy, then the hydroxy or alkoxy is not α -substituted to an N, O or S in Z;

X is O or S;

Y is absent or is selected from O, S and NR_5 ;

10 Z is absent or is selected from optionally substituted lower alkenylene, optionally substituted lower alkynylene, O, $-C(O)-$, $S(O)p$, NR_5 , $-NR_5C(O)-$ and $-C(O)NR_5-$;

x is 1, 2, 3 or 4;

v is 2, 3 or 4;

p is 1 or 2; and

15 q and r are independently 0, 1, 2 or 3, provided that q and r are not both 0, and provided that when L_1 is O, NR_5 , $-S(O)p$, $-S(O)pNR_5-$, $-C(X)Y-$ or $-L_3-Q-L_4-Q'-L_5-$ and R_3 and R_{3a} taken together form O or S, then R_2 and R_{2a} are independently selected from hydrogen, alkyl, aminoalkyl, alkylaminoalkyl, alkoxy, alkoxyalkyl, alkoxyaminoalkyl, cycloalkylalkylamino, benzyloxyalkyl, isopropyl, aminomethyl, methoxyethylaminomethyl, piperazin, pyrrolidin,

20 ethoxymethyl, benzyloxymethyl, methoxymethyl, isobutyl, isopropylamino or isopropylaminomethyl, provided that R_2 and R_{2a} are not each hydrogen; or when L_1 is O, NR_5 , $-S(O)p$, $-S(O)pNR_5-$, $-C(X)Y-$ or $-L_3-Q-L_4-Q'-L_5-$ and R_3 and R_{3a} taken together form O or S, then R_4 and R_{4a} taken together form O or S; or when L_1 is O, NR_5 , $-S(O)p$, $-S(O)pNR_5-$, $-C(X)Y-$ or $-L_3-Q-L_4-Q'-L_5-$ and R_3 and R_{3a} taken together form O or S, then Cy_1 is thiophen-isoxazol, thiophen-pyrazol, thiophen-oxadiazol, thiophen-thiadiazol, thiophen-triazol, thiophen-pyridin or phenyl-triazol and Cy_2 is amino-quinazolin or pyrrolo-pyridin;

25 or when L_1 is O, NR_5 , $-S(O)p$, $-S(O)pNR_5-$, $-C(X)Y-$ or $-L_3-Q-L_4-Q'-L_5-$ then R_1 and R_2 together with the carbon atoms through which R_1 and R_2 are linked form a cycloalkyl group, cycloalkenyl group, heterocyclyl group, heterocyclyl group, or heterocyclyenyl group; or R_3 and R_4 together with the carbon atoms through which R_3 and R_4 are linked form a cycloalkyl group, cycloalkenyl group, heterocyclyl group, or heterocyclyenyl group; or R_{1a} and R_{2a} are absent and R_1 and R_2 together with the carbon atoms through which R_1 and R_2 are linked form an aryl or heteroaryl group; or R_{3a} and R_{4a} are absent and R_3 and R_4 together with the carbon atoms through which R_3 and R_4 are linked form an aryl or heteroaryl group; or one or more of the pairs R_1 and R_{1a} taken together

with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; or R₂ and R_{2a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; or R₃ and R_{3a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; or R₄ and R_{4a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group;.

5 or when L₁ is O, NR₅, -S(O)p-, -S(O)pNR₅-, -C(X)Y- or -L₃-Q-L₄-Q'-L₅-, then R₁, R_{1a}, R₂, R_{2a}, R₃, R_{3a}, R₄ and R_{4a} are independently Y₁Y₂NC(O)- and Y₁ and Y₂ are independently hydrogen, optionally substituted alkoxy or optionally substituted aryloxy, but Y₁ and Y₂ are not

10 simultaneously hydrogen,

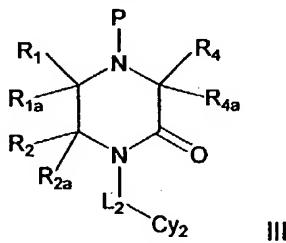
or when L₁ is O, NR₅, -S(O)p-, -S(O)pNR₅-, -C(X)Y- or -L₃-Q-L₄-Q'-L₅-, then Z is -C(O).

In another aspect, this invention is directed to a pharmaceutical composition comprising a therapeutically effective amount of the compound of formula I or formula II and a

15 pharmaceutically acceptable carrier.

In another aspect, this invention is directed to a method of treating a physiological disorder capable of being modulated by inhibiting Factor Xa comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formula I or formula II.

20 In another aspect, this invention is directed to a compound of formula III



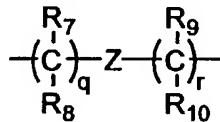
wherein P is H or a nitrogen protecting group;

25 R₁, R_{1a}, R₂, R_{2a}, R₄ and R_{4a} are independently selected from hydrogen, carboxy, alkoxy carbonyl, Y₁Y₂NC(O)-, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl, or R₁ and R_{1a}, R₂ and R_{2a} or R₄ and R_{4a} taken together form O or S; or R₁ and R₂ together with the carbon atoms through which R₁ and R₂ are linked form a cycloalkyl group, cycloalkenyl group, heterocyclil group, or heterocyclenyl group; or R_{1a} and R_{2a} are absent and R₁ and R₂ together with the carbon atoms through which R₁ and R₂ are linked form an aryl or heteroaryl group; or

30 R₁ and R_{1a} taken together with the carbon atom through which they are linked form a 3 to 7

membered cycloalkyl or cycloalkenyl group; or R₂ and R_{2a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; or R₄ and R_{4a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group;

5 L₂ is absent or a group of formula



Cy₂ is selected from optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocyclyl, optionally substituted heterocyclenyl, optionally substituted fused arylcycloalkyl, optionally

10 substituted fused arylcycloalkenyl, optionally substituted fused arylheterocyclyl, optionally substituted fused arylheterocyclenyl, optionally substituted fused heteroarylcyloalkyl, optionally substituted fused heteroarylcyloalkenyl, optionally substituted fused heteroarylheterocyclyl and optionally substituted fused heteroarylheterocyclenyl;

R₅ is hydrogen, optionally substituted alkyl, optionally substituted aralkyl, optionally substituted heteroaralkyl, R₆O(CH₂)v-, R₆O₂C(CH₂)x-, Y₁Y₂NC(O)(CH₂)x-, or Y₁Y₂N(CH₂)v-;

R₆ is hydrogen, optionally substituted alkyl, optionally substituted aralkyl or optionally substituted heteroaralkyl;

Y₁ and Y₂ are independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, optionally substituted aryl, optionally substituted aralkyl or

20 optionally substituted heteroaralkyl, or Y₁ and Y₂ taken together with the N through which Y₁ and Y₂ are linked form a monocyclic heterocyclyl;

R₇, R₈, R₉ and R₁₀ are independently selected from hydrogen, hydroxy, alkoxy, optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted aralkyl and optionally substituted heteroaralkyl, provided that only one of R₇ and R₈

25 or one of R₉ and R₁₀ is hydroxy or alkoxy, and further provided when R₇, R₈, R₉ and R₁₀ is hydroxy or alkoxy, then the hydroxy or alkoxy is not α -substituted to a N, O or S in Z;

Z is absent or is selected from optionally substituted lower alkenylene, optionally substituted lower alkynylene, O, S(O)p, -C(O)-, NR₅, -NR₅C(O)- and -C(O)NR₅-;

x is 1, 2, 3 or 4;

30 v is 2, 3 or 4; and

q and r are independently 0, 1, 2 or 3, provided that q and r are not both 0,

which is an intermediate useful in the preparation of the compound of formula I or formula II

DETAILED DESCRIPTION OF THE INVENTION

Definitions

As used above, and throughout the description of the invention, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

5 "Derivative" means a chemically modified compound wherein the modification is considered routine by the ordinary skilled chemist, such as an ester or an amide of an acid, protecting groups, such as a benzyl group for an alcohol or thiol, and tert-butoxycarbonyl group for an amine.

10 "Patient" includes both human and other mammals.

10 "Alkyl" means an aliphatic hydrocarbon group, which may be straight or branched chain, having about 1 to about 20 carbon atoms in the chain. Preferred alkyl groups have 1 to about 12 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear alkyl chain. "Lower alkyl" means about 1 to about 4 carbon atoms in the chain which may be straight or branched. The alkyl may be

15 substituted with one or more "alkyl group substituents" which may be the same or different, and include halo, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, hydroxy, oxime, alkylthio, alkylsulfinyl, alkylsulfonyl, arylthio, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylalkylthio, heteroarylalkylsulfinyl, heteroarylalkylsulfonyl, isourea, guanidino, acylhydrazino, alkoxy, amino, carbamoyl, acylamino, aroylamino, carboxy, alkoxy carbonyl, aralkyloxycarbonyl and heteroaralkyloxycarbonyl.

20 Representative alkyl groups include methyl, trifluoromethyl, cyclopropylmethyl, cyclopentylmethyl, ethyl, n-propyl, i-propyl, n-butyl, t-butyl, n-pentyl, 3-pentyl, methoxyethyl, carboxymethyl, methoxycarbonylethyl, benzyloxycarbonylmethyl, and pyridylmethyloxycarbonylmethyl.

25 "Alkenyl" means a straight or branched aliphatic hydrocarbon group containing a carbon-carbon double bond and having about 2 to about 15 carbon atoms in the chain. Preferred alkenyl groups have 2 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear alkenyl chain. "Lower alkenyl" means about 2 to about 4 carbon atoms in the chain which may be straight or branched. The alkenyl group may be substituted by one or more alkyl group

30 substituents as defined herein. Representative alkenyl groups include ethenyl, propenyl, n-but enyl, i-but enyl, 3-methylbut-2-enyl, n-pentenyl, heptenyl, octenyl, decenyl, and the like.

"Alkylene" means a straight or branched bivalent hydrocarbon chain having from 1 to about 20 carbon atoms. The preferred alkylene groups are the lower alkylene groups having from 1 to about 6 carbon atoms. Alkylene may be substituted with 1 or more alkyl group

substituents as defined herein. Representative alkylene groups include methylene, ethylene, and the like.

"Alkenylene" means a bivalent group derived from a straight or branched chain hydrocarbon containing at least one carbon-carbon triple bond. The preferred alkenylene groups are the lower alkenylene groups having from 1 to about 6 carbon atoms. Alkenylene group may be substituted by one or more alkyl group substituents as defined herein. Representative alkenylene groups include -CH=CH-, -CH₂CH=CH-, -C(CH₃)=CH-, -CH₂CH=CHCH₂-, and the like.

"Alkynylene" means a bivalent group derived from a straight or branched chain hydrocarbon containing at least one carbon-carbon double bond. Preferred alkynylene groups are the lower alkynylene groups having from 1 to about 6 carbon atoms. Alkynylene may be substituted by one or more alkyl group substituents as defined herein. Representative alkynylene include —CH:CH—, —CH:CH-CH₂—, —CH:CH-CH(CH₃)—, and the like.

15 "Aralkylamino" means a (arylalkyl)(Y₂)N- group wherein the arylalkyl portion and Y₂ are as herein defined.

"Heteroaralkylamino" means a (heteroaralkyl)(Y₂)N- group wherein the heteroaralkyl portion and Y₂ are as defined herein.

20 "Heterocyclalkyl" means a heterocycl-alkylene- group wherein the heterocycl portion and alkylene portion are as defined herein.

"Heterocyclalkylamino" means a (heterocyclalkyl)(Y₂)N- group wherein the heterocyclalkyl portion and Y₂ are as defined herein.

"Heterocyclenylalkyl" means a heterocyclenyl-alkylene- group wherein the heterocyclenyl portion and alkylene portion are as defined herein.

25 "Heterocyclenylalkylamino" means a (heterocyclenylalkyl)(Y₂)N- group wherein the heterocyclenylalkyl portion and Y₂ are as defined herein.

"Alkoxyalkyl" means an alkoxy-alkylene- group wherein the alkoxy portion and alkylene portion are as defined herein.

30 "Alkylthioalkyl" means an alkylthio-alkylene- group wherein the alkylthio portion and alkylene portion are as defined herein.

"Alkylsulfinylalkyl" means an alkylsulfinyl-alkylene- group wherein the alkylsulfinyl portion and alkylene portion are as defined herein.

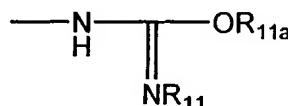
"Alkylsulfonylalkyl" means an alkylsulfonyl-alkylene- group wherein the alkylsulfonyl portion and alkylene portion are as defined herein.

"Acylalkyl" means an acyl-alkylene- group wherein the acyl portion and alkylene portion are as defined herein.

"Acylaminoalkyl" means an acyl-NH-alkylene- group wherein the acyl portion and alkylene portion are as defined herein.

5 "Carbamoylalkyl" means an carbamoyl-alkylene- group wherein the carbamoyl portion and alkylene portion are as defined herein.

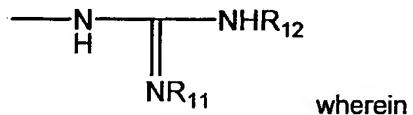
"Heterocyclalkyloxycarbonyl" means a heterocyclalkyl-O-C(O)- group wherein the heterocyclalkyl portion is as defined herein.



"Isourea" means a group of formula

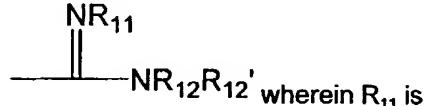
10 herein and R_{11a} is hydrogen, optionally substituted lower alkyl, optionally substituted aryl, or optionally substituted heteroaryl.

"Acylhydrazino" means a group of formula Y₁Y₂N-NHC(O)-, wherein Y₁ and Y₂ are as defined herein.



"Guanidino" or "guanidine" means a group of formula

15 R₁₁ and R₁₂ are as defined herein.



"Amidino" or "amidine" means a group of formula wherein R₁₁ is selected from hydrogen, R₆O₂C-, R₆O-, R₆C(O)-, cyano, optionally substituted lower alkyl, nitro or Y₁Y₂N- and R₁₂ and R_{12'} are independently selected from hydrogen, optionally substituted lower alkyl, optionally substituted aralkyl and optionally substituted heteroaralkyl. Preferred amidino groups are those in which R₁₁ is hydrogen, R₆O, or optionally substituted lower alkyl and R₁₂ is as defined above. Most preferred amidino groups are those in which R₁₁ and R₁₂ are hydrogen.

20 "Carbamate" means a group of formula Y₁Y₂C(O)NH- wherein Y₁ is as defined herein; Y₂ is selected from optionally substituted alkoxy or optionally substituted aryloxy. "Alkylcarbamate" means a group of formula Y₁Y₂C(O)NH- wherein Y₁ and Y₂ are independently alkyl. More preferred alkylcarbamate groups are methylcarbamate, ethylcarbamate, t-butylcarbamate, benzylcarbamate and phenylcarbamate.

"Aminoalkylamino" means a Y₁Y₂N-alkylene-(Y₂)N- group wherein Y₁, Y₂ and alkylene are as defined herein.

25 "Aryloxycarbonylalkyl" means a aryl-O-C(O)-alkylene group wherein the aryl portion and alkylene portion are as defined herein.

"Heteroaryloxycarbonylalkyl" means a heteroaryl-O-C(O)-alkylene group wherein the heteroaryl portion and alkylene portion are as defined herein.

"Heterocycloxy carbonylalkyl" means a heterocyclyl-O-C(O)-alkylene group wherein the heterocyclyl portion and alkylene portion are as defined herein.

5 "Heterocyclenylloxycarbonylalkyl" means a heterocyclenyl-O-C(O)-alkylene group wherein the heterocyclenyl portion and alkylene portion are as defined herein.

"Basic nitrogen atom" means an sp^2 or sp^3 hybridized nitrogen atom having a non-bonded pair of electrons which is capable of being protonated. Examples of basic nitrogen atoms, which may be optionally substituted where possible, include those in heteroaryl,

10 heterocyclyl, heterocyclenyl, fused arylheterocyclyl, fused arylheterocyclenyl, fused heteroarylcyloalkyl, fused heteroarylcyloalkenyl, fused heteroarylheterocyclyl, fused heterocyclylheterocyclenyl, imino, amino, isourea, acylhydrazino, guanidino and amidino groups.

15 "Cycloalkyl" means a non-aromatic mono- or multicyclic hydrocarbon ring system of about 3 to about 10 carbon atoms. Representative monocyclic cycloalkyl rings include cyclopentyl, cyclohexyl, cycloheptyl, and the like. Representative multicyclic cycloalkyl rings include decalinyl, norbornyl, adamantyl, and the like. The cycloalkyl group is optionally substituted with one or more "cycloalkyl group substituents" which may be the same or different, where "cycloalkyl group substituent" includes oxo (O=), thioxo (S=), methylene (H₂C=), oxime (HO-N=), alkyl, aryl, heteroaryl, heterocyclyl, heterocyclenyl, cycloalkyl, cycloalkenyl, acylhydrazino, aralkyl, heteroaralkyl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxy carbonyl, aryloxycarbonyl, aralkoxycarbonyl, acylamino, aroylamino, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, amidino, 25 amino, carbamoyl, or sulfamoyl. Preferred cycloalkyl group substituents are amino and amidino.

30 "Cycloalkenyl" means a non-aromatic monocyclic or multicyclic hydrocarbon ring system containing a carbon-carbon double bond and having about 3 to about 10 carbon atoms. The cycloalkenyl group is optionally substituted by one or more cycloalkyl group substituents as defined herein. Representative monocyclic cycloalkenyl rings include cyclopentenyl, cyclohexenyl or cycloheptenyl, and the like. A representative multicyclic cycloalkenyl ring is norbornylenyl. Preferred cycloalkenyl group substituents are amino and amidino.

"Carboxy" means a group of formula HO(O)C- (carboxylic acid group).

35 "Heterocyclyl" means a non-aromatic saturated monocyclic or multicyclic ring system of about 3 to about 10 ring atoms wherein the ring system contains one or more element(s) other

than carbon. Preferred heterocycll comprise about 5 to about 7 ring atoms, more preferred 5 to 6 ring atoms, wherein one or two of the ring atoms is/are independently selected from oxygen, nitrogen or sulfur respectively. "Aza", "oxa" or "thia", when used as a prefix before heterocycll means that the ring system contains at lease one nitrogen, oxygen and sulfur atom. For 5 example, "azaheterocycll" means a heterocycll group wherein one or more of the atoms in the ring system is/are nitrogen. The heterocycll group is optionally substituted with one or more heterocycll group substituents which may be the same or different, where " heterocycll group substituent" includes oxo (O=), thioxo (S=), methylene (H₂C=), oxime (HO-N=), alkyl, aryl, heteroaryl, heterocycll, heterocyclenyl, cycloalkyl, cycloalkenyl, acylhydrazino, aralkyl, 10 heteroaralkyl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxy carbonyl, aryloxy carbonyl, aralkoxy carbonyl, acylamino, aroylamino, alkylsulfonyl, arylsulfonyl, heteroaryl sulfonyl, alkylsulfinyl, arylsulfinyl, heteroaryl sulfinyl, alkylthio, arylthio, heteroaryl thio, aralkylthio, heteroaralkylthio, amino, carbamoyl, and sulfamoyl. Preferred heterocycll group substituents include amino, amidino, halogen, hydroxy, 15 alkoxy carbonyl alkyl and carboxy alkyl. Representative heterocycll groups include piperidyl, pyrrolidinyl, piperazinyl, pyrazolidinyl, imidazolinyl, hexamethyleneimine, homopiperazine, tetrahydrofuryl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,3-dioxolanyl, 1,4-dioxanyl, 1,4-dithianyl, 1,3,5-trithianyl, tetrahydrothienyl, tetrahydrothiopyranyl, quinuclidinyl, and the like. The thio or nitrogen moiety of the heterocycll may also be optionally oxidized to the 20 corresponding S-oxide, S,S-dioxide or N-oxide.

"Heterocyclenyl" means a heterocycll group as defined herein which contains at least one carbon-carbon or carbon-nitrogen double bond. "Aza", "oxa" or "thia", when used as a prefix before heterocyclenyl group means that the ring system contains at lease one nitrogen, oxygen or sulfur atom respectively. The heterocyclenyl group is optionally substituted with one 25 or more heterocycll group substituents as defined herein. Representative heterocyclenyl groups include 2H-pyrrolyl, 2-pyrrolinyl, 3-pyrrolinyl, 2-imidazolinyl, 2-pyrazolinyl, 2H-pyranyl, 1,2-dihydropyridyl, 1,4-dihydropyridyl, 1,2,3,4- tetrahydropyridyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like. Preferred heterocyclenyl group substituents include amino, amidino, halogen, hydroxy, oxo, thioxo, methylene, oxime, alkoxy carbonyl alkyl and 30 carboxy alkyl. The thio or nitrogen moiety of the heterocycll may also be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide.

"Aryl" means a 6 to 10 membered aromatic monocyclic or multicyclic hydrocarbon ring system. The aryl group is optionally substituted with one or more "aryl group substituents" which may be the same or different, where "aryl group substituent" includes alkyl, aryl, 35 heteroaryl, heterocycll, heterocyclenyl, cycloalkyl, cycloalkenyl, acylhydrazino, aralkyl,

heteroaralkyl, aryldiazo, heteroaryldiazo, hydroxy, alkylcarbamate, acylhydrazino, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, acylamino, aroylamino, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylthio, arylthio, heteroarylthio, aralkylthio,

5 heteroaralkylthio, arylazo, heteroarylazo, amino, amidino, alkylamino, carbamoyl, and sulfamoyl. Preferred aryl groups are optionally substituted phenyl or optionally substituted naphthyl. Preferred aryl group substituents include alkyl, aryl, heteroaryl, heterocyclyl, heterocyclenyl, cycloalkyl, cycloalkenyl, acylhydrazino, carboxy, sulfamoyl, alkylcarbamate, hydroxy, acyl, aroyl, halo, nitro, cyano, alkoxycarbonyl, acylamino, alkylthio, alkylamino, amino,

10 carbamoyl, thiocarbamoyl and amidino.

"Heteroaryl" means about a 5- to about a 10- membered aromatic monocyclic or multicyclic ring system wherein one or more of the atoms in the ring system is/are element(s) other than carbon. Preferred heteroaryl groups contain one to about 4 heteroatoms selected from oxygen, nitrogen and sulfur. "Aza", "oxa" or "thia", when used as a prefix before heteroaryl

15 means that the ring system contains at least one nitrogen, oxygen or sulfur atom. The heteroaryl group is optionally substituted with one or more aryl group substituents as defined herein. Representative heteroaryl groups include pyrrolyl, pyrazinyl, furyl, thienyl, pyridyl, pyrimidyl, pyridazinyl, isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, triazolyl, oxadiazolyl, thiadiazolyl, thienopyridyl, thienopyrrolyl, thieno[3,2-d]pyrimidyl, pyrrolopyridyl, furanopyridyl,

20 furazanyl, quinoxaliny, quinazolinyl, quinolizinyl, imidazo[1,2-a]pyridyl, phthalazinyl, imidazo[2,1-b]thiazolyl, benzofuranyl, indolyl, isoindolyl, indolizinyl, indazolyl, azaindolyl, benzimidazolyl, benzothienyl, benzisoxazolyl, benzothiazolyl, purinyl, benzotriazolyl, 1,8-naphthyridinyl, pteridinyl, quinolinyl, imidazolyl, isoquinolinyl, cinnolinyl, triazinyl, benzotriazinyl, and the like. Preferred heteroaryl group substituents include hydrogen, alkyl, aryl, heteroaryl,

25 heterocyclyl, heterocyclenyl, cycloalkyl, cycloalkenyl, acylhydrazino, hydroxy, acyl, aroyl, halo, nitro, cyano, carboxy, acylhydrazino, alkoxycarbonyl, acylamino, alkylthio, alkylamino, amino, carbamoyl, thiocarbamoyl and amidino. When the heteroaryl groups contains a nitrogen atom, the nitrogen atom may be oxidized to the N-oxide.

"Fused arylcycloalkyl" means a fused aryl and cycloalkyl, wherein the aryl and cycloalkyl portions are as defined herein. Preferred fused arylcycloalkyls groups are those wherein the aryl thereof is phenyl and the cycloalkyl consists of about 5 to about 6 carbon atoms. Representative fused phenylcycloalkyl groups include 1,2,3,4-tetrahydronaphthyl, indanyl, and the like. The fused arylcycloalkyl group is optionally substituted with one or more fused arylcycloalkyl group substituents selected from, alkyl, aryl, heteroaryl, heterocyclyl, heterocyclenyl, cycloalkyl, cycloalkenyl, acylhydrazino, aralkyl, heteroaralkyl, aryldiazo,

heteroaryldiazo, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, acylamino, aroylamino, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, arylazo, heteroarylazo, amino,

5 alkylamino, carbamoyl and sulfamoyl. The cycloalkyl moiety is further optionally substituted with oxo (O=), thioxo (S=), methylene (H₂C=), or oxime (HO-N=). Preferred fused phenylcycloalkyl group substituents include alkyl, aryl, heteroaryl, heterocyclyl, heterocyclenyl, cycloalkyl, cycloalkenyl, acylhydrazino, hydroxy, acyl, aroyl, halo, nitro, cyano, alkoxycarbonyl, acylamino, alkylthio, alkylamino, amino, carbamoyl, thiocarbamoyl and amidino.

10 "Fused arylcycloalkenyl" means a fused aryl and cycloalkenyl, wherein the aryl and cycloalkenyl portions are as defined herein. Preferred fused arylcycloalkenyl groups are those wherein the aryl thereof is phenyl and the cycloalkenyl consists of about 5 to about 6 carbon atoms. The fused arylcycloalkenyl is optionally substituted with one or more fused arylcycloalkyl group substituents as defined herein. Representative fused phenylcycloalkenyl groups include 1,2-dihydronaphthylenyl, indenyl, and the like. The cycloalkyl moiety is further optionally substituted with oxo (O=), thioxo (S=), methylene (H₂C=), oxime (HO-N=). Preferred substituents include alkyl, aryl, heteroaryl, heterocyclyl, heterocyclenyl, cycloalkyl, cycloalkenyl, acylhydrazino, hydroxy, acyl, aroyl, halo, nitro, cyano, alkoxycarbonyl, acylamino, alkylthio, alkylamino, amino, carbamoyl, thiocarbamoyl and amidino.

15 20 "Fused arylheterocyclyl" means a fused aryl and heterocyclyl, wherein the aryl and heterocyclyl portions are as defined herein. Preferred fused arylheterocyclyl groups are those wherein the aryl portion thereof is phenyl and the heterocyclyl portion consists of about 5 to about 7 ring atoms, more preferred 5 to 6 ring atoms, wherein one or two of the ring atoms is/are independently selected from oxygen, nitrogen and sulfur. "Aza", "oxa" or "thia", when used as a prefix before the heterocyclyl portion of the fused arylheterocyclyl means that the heterocyclyl contains at least one nitrogen, oxygen or sulfur atom. Representative preferred fused phenylheterocyclyl ring systems include indolinyl, 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 2,3-dihydrobenzofuran, 1H-2,3-dihydroisoindolyl, 2,3-dihydrobenz[f]isoindolyl, 1,2,3,4-tetrahydrobenz[g]isoquinolinyl, and the like. The fused phenylheterocyclyl group is optionally substituted with one or more fused phenylcycloalkyl group substituents as defined herein. The heterocyclyl portion is further optionally substituted with oxo (O=), thioxo (S=), methylene (H₂C=) or oxime (HO-N=). Preferred substituents include alkyl, aryl, heteroaryl, heterocyclyl, heterocyclenyl, cycloalkyl, cycloalkenyl, acylhydrazino, hydroxy, acyl, aroyl, halo, nitro, cyano, alkoxycarbonyl, acylamino, alkylthio, alkylamino, amino,

carbamoyl, thiocarbamoyl and amidino. The nitrogen or sulphur atom of the heterocyclyl may also be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide.

"Fused arylheterocyclenyl" means a fused aryl and heterocyclenyl, wherein the aryl and heterocyclenyl portions are as defined herein. "Aza", "oxa" or "thia", when used as a prefix before the heterocyclenyl portion of the fused arylheterocyclenyl group means that the heterocyclenyl portion contains at least one nitrogen, oxygen or sulfur atom. Preferred fused arylheterocyclenyl groups are those wherein the aryl thereof is phenyl and the heterocyclenyl consists of about 5 to 6 ring atoms wherein one or two of the ring atoms is/are independently selected from oxygen, nitrogen and sulfur. Representative preferred fused arylheterocycloalkenyl ring systems include 3H-indoliny, 3H-quinazolin-4-one, 1,1-dioxo-benzo[d]isothiazolyl, 1H-2-oxoquinolyl, 2H-1-oxoisoquinolyl, and the like. The fused arylheterocyclenyl group is optionally substituted with one or more fused arylcycloalkyl group substituents as defined herein. The heterocyclenyl portion is further optionally substituted with oxo (O=), thioxo (S=), methylene (H₂C=) or oxime (HO-N=). Preferred substituents include alkyl, aryl, heteroaryl, heterocyclenyl, cycloalkyl, cycloalkenyl, acylhydrazino, hydroxy, acyl, aroyl, halo, nitro, cyano, alkoxy carbonyl, acylamino, alkylthio, alkylamino, amino, carbamoyl, thiocarbamoyl and amidino. The nitrogen or sulphur atom of the heterocyclenyl is optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide.

"Fused heteroaryl cycloalkyl" means a fused heteroaryl and cycloalkyl, wherein the heteroaryl and cycloalkyl portions are as defined herein. "Aza", "oxa" or "thia", when used as a prefix before the heteroaryl portion of the fused heteroaryl cycloalkyl group means that the heteroaryl portion contains at least one nitrogen, oxygen or sulfur atom. Preferred fused heteroaryl cycloalkyl groups are those wherein the heteroaryl portion thereof consists of about 5 to about 6 ring atoms in which one or two of the ring atoms are independently selected from oxygen, nitrogen and sulfur and the cycloalkyl consists of about 5 to about 6 ring atoms. Representative preferred fused heteroaryl cycloalkyl groups include 5,6,7,8-tetrahydroisoquinolyl, 5,6,7,8-tetrahydroquinoxalinyl, 5,6,7,8-tetrahydroquinazolyl, 4,5,6,7-tetrahydro-1H-benzimidazolyl, 4,5,6,7-tetrahydrobenzoxazolyl, 1H-4-oxa-1,5-diazanaphthalen-2-onyl, 1,3-dihydroimidazole-[4,5]-pyridin-2-onyl, 5,6,7,8-tetrahydrobenzothiazolyl, 5,6-dihydro-4H-benzothiazol-7-one, and the like. The fused heteroaryl cycloalkyl group is optionally substituted with one or more fused phenylcycloalkyl group substituents as defined herein. The cycloalkyl moiety is further optionally substituted with oxo (O=), thioxo (S=), methylene (H₂C=) or oxime (HO-N=). Preferred substituents include alkyl, aryl, heteroaryl, heterocyclenyl, heterocyclenyl, cycloalkyl, cycloalkenyl, acylhydrazino, hydroxy, acyl, aroyl, halo, nitro, cyano, alkoxy carbonyl, acylamino, alkylthio, alkylamino, amino, carbamoyl, thiocarbamoyl and amidino.

The nitrogen atom of the heteroaryl portion of the fused heteroarylcy cloalkyl group is optionally oxidized to the N-oxide.

"Fused heteroarylcy cloalkenyl" means a 5- or 6-membered heteroaryl fused with a cycloalkenyl ring. "Aza", "oxa" or "thia", when used as a prefix before the heteroaryl portion of

5 the fused heteroarylcy cloalkenyl means that the cycloalkenyl contains at least one nitrogen, oxygen or sulfur atom. Preferred fused heteroarylcy cloalkenyls are those wherein the heteroaryl thereof consists of about 5 to about 6 ring atoms in which one or two of the ring atoms are independently selected from oxygen, nitrogen and sulfur and the cycloalkenyl consists of about 5 to about 6 ring atoms. Representative preferred fused

10 heteroarylcy cloalkenyl include 5,6-dihydroisoquinolyl, 5,6-dihydroquinoxalinyl, 5,6-dihydroquinazolinyl, 4,5-dihydro-1H-benzimidazolyl, 4,5-dihydrobenzoxazolyl, and the like.

The fused heteroarylcy cloalkenyl is optionally substituted with one or more fused phenylcy cloalkyl group substituents as defined herein. The cycloalkenyl moiety is further optionally substituted with oxo (O=), thioxo (S=), methylene (H₂C=) or oxime (HO-N=).

15 Preferred substituents include alkyl, aryl, heteroaryl, heterocyclyl, heterocyclenyl, cycloalkyl, cycloalkenyl, acylhydrazino, hydroxy, acyl, aroyl, halo, nitro, cyano, alkoxy carbonyl, acylamino, alkylthio, alkylamino, amino, carbamoyl, thiocarbamoyl and amidino. The nitrogen atom of the heteroaryl portion of the fused heteroarylcy cloalkyl is optionally oxidized to the N-oxide.

"Fused heteroarylheterocyclyl" means a heteroaryl ring fused with a heterocyclyl ring

20 wherein the heteroaryl and heterocyclyl portions are as defined herein. "Aza", "oxa" or "thia", when used as a prefix before the heteroaryl or heterocyclyl portion of the fused heteroarylheterocyclyl group means that the heteroaryl or heterocyclyl portion contains at least one nitrogen, oxygen or sulfur atom. Preferred fused heteroarylheterocyclyl groups are ring systems wherein one or two of the ring atoms of the heteroaryl are independently selected from oxygen, nitrogen and sulfur and the heterocyclyl portion consists of about 5 to about 6 ring atoms in which one or two of the ring atoms are independently selected from oxygen, nitrogen and sulfur. Representative fused heteroarylheterocyclyl groups include 4,7-dihydro-5H-thiazolo[5,4-c]pyridin-6-one, 5,6,7,8-tetrahydro-thiazolo[4,5-c]azepin-4-one, 2,3-dihydro-1H pyrrol[3,4-b]quinolin-2-yl, 1,2,3,4-tetrahydrobenz [b][1,7]naphthyridin-2-yl,

30 1,2,3,4-tetrahydrobenz [b][1,6]naphthyridin-2-yl, 1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indol-2-yl, 1,2,3,4-tetrahydro-9H-pyrido[4,3-b]indol-2-yl, 2,3,-dihydro-1H-pyrrolo[3,4-b]indol-2-yl, 1H-2,3,4,5-tetrahydroazepino[3,4-b]indol-2-yl, 1H-2,3,4,5-tetrahydroazepino[4,3-b]indol-3-yl, 1H-2,3,4,5-tetrahydroazepino[4,5-b]indol-2-yl, 5,6,7,8-tetrahydro[1,7]naphthyridinyl, 1,2,3,4-tetrahydro[2,7]naphthyridyl, 2,3-dihydro[1,4]dioxino[2,3-b]pyridyl, 2,3-dihydro[1,4]dioxino[2,3-b]pyridyl, 3,4-dihydro-2H-1-oxa-4,6-diazanaphthalenyl,

4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridyl, 6,7-dihydro-5,8-diazanaphthalenyl, and the like.

The fused heteroarylheterocyclyl group is optionally substituted with one or more fused arylcycloalkyl group substituents as defined herein. The heterocyclyl portion is further optionally substituted with oxo (O=), thioxo (S=), methylene (H₂C=) or oxime (HO-N=).

5 Preferred substituents include alkyl, aryl, heteroaryl, heterocyclyl, heterocyclenyl, cycloalkyl, cycloalkenyl, acylhydrazino, hydroxy, acyl, aroyl, halo, nitro, cyano, alkoxy carbonyl, acylamino, alkylthio, alkylamino, amino, carbamoyl, thiocarbamoyl and amidino. The nitrogen atom of the heteroaryl portion is optionally oxidized to the N-oxide. The nitrogen or sulphur atom of the heterocyclyl portion is optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide.

10 "Fused heteroarylheterocyclenyl" means a fused heteroaryl and heterocyclenyl, wherein the heteroaryl and heterocyclenyl portions are as defined herein. "Aza", "oxa" or "thia", when used as a prefix before the heteroaryl or heterocyclenyl portion of the fused heteroarylheterocyclenyl group means that the heteroaryl or heterocyclenyl portion contains at least one nitrogen, oxygen or sulfur atom. Preferred fused heteroaryl cycloalkenyl groups are 15 ring systems wherein the heteroaryl portion thereof consists of about 5 to about 6 ring atoms in which one or two of the ring atoms are independently selected from oxygen, nitrogen and sulfur and the heterocyclenyl portion consists of about 5 to about 6 ring atoms in which one or two of the ring atoms are independently selected from oxygen, nitrogen and sulfur. Representative fused heteroarylheterocyclenyl groups include 7,8-dihydro[1,7]naphthyridinyl, 1,2-

20 dihydro[2,7]naphthyridinyl, 6,7-dihydro-3H-imidazo[4,5-c]pyridyl, and the like. The fused heteroarylheterocyclenyl group is optionally substituted with one or more fused arylcycloalkyl group substituents as defined herein. The heterocyclenyl portion is further optionally substituted with oxo (O=), thioxo (S=), methylene (H₂C=) or oxime (HO-N=). Preferred substituents include alkyl, aryl, heteroaryl, heterocyclyl, heterocyclenyl, cycloalkyl, cycloalkenyl, 25 acylhydrazino, hydroxy, acyl, aroyl, halo, nitro, cyano, alkoxy carbonyl, acylamino, alkylthio, alkylamino, amino, carbamoyl, thiocarbamoyl and amidino. The nitrogen atom of the heteroaryl portion is optionally oxidized to the N-oxide. The nitrogen or sulphur atom of the heterocyclenyl is optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide.

30 "Aralkyl" means an aryl-alkyl- group in which the aryl portion and alkyl portion are as defined herein. Preferred aralkyl groups contain a lower alkyl moiety. Representative aralkyl groups include benzyl, 2-phenethyl and naphthlenemethyl.

35 "Heteroaralkyl" means a heteroaryl-alkyl- group in which the heteroaryl portion and alkyl portion are as defined herein. Preferred heteroaralkyl groups contain a lower alkyl moiety. Representative heteroaralkyl groups may contain thiienylmethyl, pyridylmethyl, imidazolylmethyl and pyrazinylmethyl.

"Aralkenyl" means an aryl-alkenyl- group in which the aryl portion and alkenyl portion are as defined herein. Preferred aralkenyl groups contain a lower alkenyl moiety. An representative aralkenyl group is 2-phenethenyl.

"Heteroaralkenyl" means a heteroaryl-alkenyl- group in which the heteroaryl portion and alkenyl portion are as defined herein. Preferred heteroaralkenyls contain a lower alkenyl moiety. Representative heteroaralkenyl groups may contain thienylethenyl, pyridylethenyl, imidazolylethenyl and pyrazinylethenyl.

"Hydroxyalkyl" means a HO-alkylene- group in which the alkylene portion is as defined herein. Preferred hydroxyalkyl groups contain lower alkylene. Representative hydroxyalkyl groups include hydroxymethyl and 2-hydroxyethyl.

"Acyl" means an H-CO- or alkyl-CO- group in which the alkyl portion is as defined herein. Preferred acyl groups contain a lower alkyl. Representative acyl groups include formyl, acetyl, propanoyl, 2-methylpropanoyl, butanoyl and palmitoyl.

"Aroyl" means an aryl-CO- group in which the aryl portion is as defined herein.

15 Representative aroyl groups include benzoyl and 1- and 2-naphthoyl.

"Aryldiazo" means an aryl-N=N- group in which the aryl portion is as defined herein. Representative aryldiazo groups include phenyldiazo and naphthyldiazo.

"Heteroaroyl" means a heteroaryl-CO- group in which the heteroaryl portion is as defined herein. Representative heteroaryl groups include thiophenoyl and pyridinoyl.

20 "Heteroaryldiazo" means a heteroaryl-N=N- group in which the heteroaryl group is as defined herein. Representative heteroaryldiazo groups include pyridyldiazo and thienyldiazo.

"Alkoxy" means an alkyl-O- group in which the alkyl portion is as defined herein. Representative alkoxy groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy and heptoxy.

25 "Aryloxy" means an aryl-O- group in which the aryl portion is as defined herein. Representative aryloxy groups include phenoxy and naphthoxy.

"Aralkyloxy" means an aralkyl-O- group in aralkyl portion is as defined herein. Representative aralkyloxy groups include benzyloxy and 1- or 2-naphthalenemethoxy.

30 "Alkylthio" means an alkyl-S- group in which alkyl portion is as defined herein. Representative alkylthio groups include methylthio, ethylthio, i-propylthio and heptylthio.

"Arylthio" means an aryl-S- group in which the aryl portion is as defined herein. Representative arylthio groups include phenylthio and naphthylthio.

"Aralkylthio" means an aralkyl-S- group in which the aralkyl portion is as defined herein. A representative aralkylthio group is benzylthio.

"Amino" means a group of formula Y_1Y_2N - wherein Y_1 and Y_2 are defined herein.

Preferred amino groups include amino (H_2N -), methylamino, dimethylamino, diethylamino, benzylamino, phenethylamino, 5-aminoindolyl, 2-amino-2-thiazolinyl, N-(2-aminoethyl)morpholine, 2(aminomethyl)pyridine, or 4(aminomethyl)pyridine.

5 "Aminoalkyl" means a Y_1Y_2N -alkylene- group wherein Y_1 , Y_2 and the alkylene portion are defined herein.

"Alkoxy carbonyl" and "alkyloxycarbonyl" means an alkyl-O-CO- group wherein the alkyl portion is as defined herein. Representative alkoxy carbonyl groups include methoxycarbonyl, ethoxycarbonyl, or t-butyloxycarbonyl.

10 "Heterocyclalkyloxycarbonyl" means an heterocyclalkyloxycarbonyl group wherein the heterocycl portion and alkyloxycarbonyl portion are as defined herein. A representative example of a heterocyclalkyloxycarbonyl group is pyrrolidinylethoxycarbonyl.

"Heterocyclenylalkyloxycarbonyl" means an heterocyclenyl-alkyloxycarbonyl group wherein the heterocyclenyl portion and alkyloxycarbonyl portion are as defined herein. A

15 representative example of a heterocyclenylalkyloxycarbonyl group is pyrrolinylethoxycarbonyl.

"Heteroaralkyloxycarbonyl" means an heteroaryl-alkyloxycarbonyl group wherein the heteroaryl portion and alkyloxycarbonyl portion are as defined herein. A representative example of a heteroaralkyloxycarbonyl group is pyridylethoxycarbonyl.

20 "Arylalkyloxycarbonyl" means an aryl-alkyloxycarbonyl group wherein the aryl portion and alkyloxycarbonyl portion are as defined herein. A representative example of a aralkyloxycarbonyl group is phenylethoxycarbonyl.

"Cycloalkylalkyloxycarbonyl" means a cycloalkyl-alkyloxycarbonyl group wherein the cycloalkyl portion and alkyloxycarbonyl portion are as defined herein. A representative example of a ar cycloalkylalkyloxycarbonyl group is cyclohexylethoxycarbonyl.

25 "Cycloalkenylalkyloxycarbonyl" means a cycloalkenyl-alkyloxycarbonyl group wherein the cycloalkenyl portion and alkyloxycarbonyl portion are as defined herein. A representative example of a ar cycloalkenylalkyloxycarbonyl group is cyclohexenylethoxycarbonyl.

"Alkoxy carbonylalkyl" means an alkyl-O-CO-alkylene- group wherein alkyl portion and alkylene portion are defined herein.

30 "Aryloxycarbonyl" means an aryl-O-CO- group wherein aryl portion is as defined herein. Representative aryloxycarbonyl groups include phenoxy carbonyl and naphthoxycarbonyl.

"Aralkyloxycarbonyl" means an aralkyl-O-CO- group wherein aralkyl portion is as defined herein. A representative aralkyloxycarbonyl group is benzyloxycarbonyl.

"Carbamoyl" means a group of formula $Y_1Y_2NCO^-$ wherein Y_1 and Y_2 are defined herein. Representative carbamoyl groups are carbamoyl (H_2NCO^-) and dimethylaminocarbamoyl ($(Me_2NCO)^-$).

"Heterocyclalkylcarbamoyl" means a heterocyclalkylene-carbamoyl wherein the 5 heterocyclalkyl, alkylene and carbamoyl portions are as defined herein. A representative example of a heterocyclalkylene-carbamoyl group is pyrrolidinylethylcarbamoyl.

"Heterocyclenylalkylcarbamoyl" means a heterocyclenyl-alkylene-carbamoyl wherein the heterocyclenyl, alkylene and carbamoyl portions are as defined herein. A representative example of a heterocyclenylalkylene-carbamoyl group is pyrrolinylethylcarbamoyl.

10 "Heteroaralkylcarbamoyl" means a heteroaryl-alkylene-carbamoyl wherein the heteroaryl, alkylene and carbamoyl portions are as defined herein. A representative example of a heteroaralkylene-carbamoyl group is pyridinylethylcarbamoyl.

15 "Arylalkylcarbamoyl" means an aryl-alkylene-carbamoyl wherein the aryl, alkylene and carbamoyl portions are as defined herein. A representative example of an aralkylene-carbamoyl group is phenylethylcarbamoyl.

"Cycloalkylalkylcarbamoyl" means an cycloalkyl-alkylene-carbamoyl wherein the cycloalkyl, alkylene and carbamoyl portions are as defined herein. A representative example of an cycloalkylalkylcarbamoyl group is cyclohexylethylcarbamoyl.

20 "Cycloalkenylcarbamoyl" means an cycloalkenyl-alkylene-carbamoyl wherein the cycloalkenyl, alkylene and carbamoyl portions are as defined herein. A representative example of an cycloalkenylalkenylcarbamoyl group is cyclohexenylethylcarbamoyl.

"Sulfamoyl" means a group of formula $Y_1Y_2NSO_2^-$ wherein Y_1 and Y_2 are defined herein. Representative sulfamoyl groups are aminosulfamoyl ($H_2NSO_2^-$) and dimethylaminosulfamoyl ($(Me_2NSO_2)^-$).

25 "Acylamino" means an acyl-NH- group wherein the acyl portion is as defined herein.

"Aroylamino" means an aroyl-NH- group wherein the aroyl portion is as defined herein.

"Alkylsulfonyl" means an alkyl- SO_2^- group wherein the alkyl portion is as defined herein.

Preferred alkylsulfonyl groups are those in which the alkyl group is lower alkyl.

"Alkylsulfinyl" means an alkyl- SO^- group wherein the alkyl portion is as defined herein.

30 Preferred alkylsulfinyl groups are those in which the alkyl portion is lower alkyl.

"Arylsulfonyl" means an aryl- SO_2^- group wherein the aryl portion is as defined herein.

"Arylsulfinyl" means an aryl- SO^- group wherein the aryl portion is as defined herein.

"Halo" or "halogen" means fluoro, chloro, bromo, or iodo. Preferred are fluoro, chloro or bromo, and more preferred are fluoro or chloro.

"Nitrogen protecting group" means an easily removable group which is known in the art to protect an amino group against undesirable reaction during synthetic procedures and to be selectively removable. The use of N-protecting groups is well known in the art for protecting groups against undesirable reactions during a synthetic procedure and many such protecting groups are known, Cf, for example, T.H. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, 2nd edition, John Wiley & Sons, New York (1991), incorporated herein by reference. Preferred N-protecting groups are acyl, including formyl, acetyl, chloroacetyl, trichloroacetyl, o-nitrophenylacetyl, o-nitrophenoxyacetyl, trifluoroacetyl, acetoacetyl, 4-chlorobutyryl, isobutyryl, o-nitrocinnamoyl, picolinoyl, acylisothiocyanate, aminocaproyl, benzoyl and the like, and acyloxy including methoxycarbonyl, 9-fluorenylmethoxycarbonyl, 2,2,2-trifluoroethoxycarbonyl, 2-trimethylsilylethoxycarbonyl, vinyloxycarbonyl, allyloxycarbonyl, t-butyloxycarbonyl (BOC), 1,1-dimethylpropynloxycarbonyl, benzyloxycarbonyl (CBZ), p-nitrophenylsulfinyl, p-nitrobenzyloxycarbonyl, 2,4-dichlorobenzyloxycarbonyl, allyloxycarbonyl (Alloc), and the like.

15 "Compounds of the invention", and equivalent expressions, are meant to embrace compounds of general formula I or formula II as hereinbefore described, which expression includes the prodrugs, the pharmaceutically acceptable salts, and the solvates, e.g. hydrates, where the context so permits. It is understood that the activity of individual compounds of formula I or formula II will vary depending on the individual compound and assay employed.

20 Compounds of the invention as used herein includes all compounds of formula I or formula II having an in-vitro activity of greater than 10% at 3.9 μ M in the Factor Xa in vitro enzyme assay described herein. Similarly, reference to intermediates, whether or not they themselves are claimed, is meant to embrace their salts, and solvates, where the context so permits. For the sake of clarity, particular instances when the context so permits are sometimes indicated in the

25 text, but these instances are purely illustrative and it is not intended to exclude other instances when the context so permits.

30 "Prodrug" means a form of the compound of formula I or formula II which may or may not itself be biologically active but which may be converted, for example by metabolic, solvolytic, or other physiological means, to a biologically active chemical entity, and is suitable for administration to a patient without undue toxicity, irritation, allergic response, and the like, and effective for their intended use, including ketal, ester and zwitterionic forms. A prodrug is transformed in vivo to yield the parent compound of the above formula, for example by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A. C. S. Symposium Series, and in Edward B. Roche,

ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

"Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolable solvates. Representative solvates include ethanolates, methanolates, and the like. "Hydrate" is a solvate wherein the solvent molecule(s) is/are H₂O.

10 In a specific embodiment, the term "about" or "approximately" means within 20%, preferably within 10%, and more preferably within 5% of a given value or range

Where the compound of this invention is substituted with a basic moiety, acid addition salts may be formed. The acids which can be used to prepare the acid addition salts include preferably those which produce, when combined with the free base, pharmaceutically

15 acceptable salts, that is, salts whose anions are non-toxic to the patient in pharmaceutical doses of the salts, so that the beneficial effects inherent in the free base are not vitiated by side effects ascribable to the anions. Although pharmaceutically acceptable salts of said basic compounds are preferred, all acid addition salts are useful as sources of the free base form even if the particular salt, per se, is desired only as an intermediate product as, for example,

20 when the salt is formed only for purposes of purification, and identification, or when it is used as intermediate in preparing a pharmaceutically acceptable salt by ion exchange procedures.

Pharmaceutically acceptable salts within the scope of the invention are those derived from the following acids: mineral acids such as hydrochloric acid, sulfuric acid, phosphoric acid and sulfamic acid; and organic acids such as acetic acid, citric acid, lactic acid, tartaric acid, malonic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, cyclohexylsulfamic acid, quinic acid, and the like. The corresponding acid addition salts comprise the following: hydrohalides, e.g. hydrochloride and hydrobromide, sulfate, phosphate, nitrate, sulfamate, acetate, citrate, lactate, tartarate, malonate, oxalate, salicylate, propionate, succinate, fumarate, maleate,

30 methylene-bis-β-hydroxynaphthoates, gentisates, mesylates, isethionates and di-p-toluoyltartratesmethanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate, cyclohexylsulfamate and quinate, respectively.

35 Acid addition salts of the compounds of this invention are prepared by reaction of the free base with the appropriate acid by the application or adaptation of known methods. For example, the acid addition salts of the compounds of this invention are prepared either by

dissolving the free base in aqueous or aqueous-alcohol solution or other suitable solvents containing the appropriate acid and isolating the salt by evaporating the solution, or by reacting the free base and acid in an organic solvent, in which case the salt separates directly or can be obtained by concentration of the solution.

5 The compounds of this invention can be regenerated from the acid addition salts by the application or adaptation of known methods. For example, parent compounds of the invention can be regenerated from their acid addition salts by treatment with an alkali, e.g. aqueous sodium bicarbonate solution or aqueous ammonia solution.

Where the compound of the invention is substituted with an acidic moiety, base addition
10 salts may be formed. The bases which can be used to prepare the base addition salts include preferably those which produce, when combined with the free acid, pharmaceutically acceptable salts, that is, salts whose cations are non-toxic to the animal organism in pharmaceutical doses of the salts, so that the beneficial effects inherent in the free acid are not vitiated by side effects ascribable to the cations. Pharmaceutically acceptable salts, including
15 for example alkali and alkaline earth metal salts, within the scope of the invention are those derived from the following bases: sodium hydride, sodium hydroxide, potassium hydroxide, calcium hydroxide, aluminum hydroxide, lithium hydroxide, magnesium hydroxide, zinc hydroxide, ammonia, trimethylammonia, triethylammonia, ethylenediamine, n-methylglucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine,
20 chloroprocaine, diethanolamine, procaine, n-benzylphenethylamine, diethylamine, piperazine, tris(hydroxymethyl)aminomethane, tetramethylammonium hydroxide, and the like.

Metal salts of compounds of the present invention may be obtained by contacting a
hydride, hydroxide, carbonate or similar reactive compound of the chosen metal in an aqueous
or organic solvent with the free acid form of the compound. The aqueous solvent employed
25 may be water or it may be a mixture of water with an organic solvent, preferably an alcohol
such as methanol or ethanol, a ketone such as acetone, an aliphatic ether such as
tetrahydrofuran, or an ester such as ethyl acetate. Such reactions are normally conducted at
ambient temperature but they may, if desired, be conducted with heating.

Amine salts of compounds of the present invention may be obtained by contacting an
30 amine in an aqueous or organic solvent with the free acid form of the compound. Suitable
aqueous solvents include water and mixtures of water with alcohols such as methanol or
ethanol, ethers such as tetrahydrofuran, nitriles such as acetonitrile, or ketones such as
acetone. Amino acid salts may be similarly prepared.

The compounds of this invention can be regenerated from the base addition salts by the
35 application or adaptation of known methods. For example, parent compounds of the invention

can be regenerated from their base addition salts by treatment with an acid, e.g. hydrochloric acid.

As well as being useful in themselves as active compounds, salts of compounds of the invention are useful for the purposes of purification of the compounds, for example by 5 exploitation of the solubility differences between the salts and the parent compounds, side products and/or starting materials by techniques well known to those skilled in the art.

It will be appreciated that compounds useful according to the present invention may contain asymmetric centers. These asymmetric centers may independently be in either the R or S configuration. It will be apparent to those skilled in the art that certain compounds useful 10 according to the invention may also exhibit geometrical isomerism. It is to be understood that the present invention includes individual stereoisomers and mixtures thereof, including racemic mixtures, of compounds of formula I or formula II hereinabove. Such isomers can be separated from their mixtures, by the application or adaptation of known methods, for example chromatographic techniques and recrystallisation techniques, or they are separately prepared 15 from the appropriate isomers of their intermediates.

Compounds of this invention may also exhibit geometrical isomerism. Geometrical isomers include the cis and trans forms of compounds of the invention having alkenyl or alkenylenyl moieties. The present invention comprises the individual geometrical isomers and stereoisomers and mixtures thereof.

20 For the propose herein it is understood that tautermeric forms are included in the recitation of a given group, e.g., thio/mercaptop or oxo/hydroxyl.

Preferred Embodiments

Another preferred aspect of the invention is a compound of formula I, wherein q is 0 and 25 Z is absent.

Another preferred aspect of the invention is a compound of formula I, wherein q is 0, r is 1 and Z is absent.

Another preferred aspect of the invention is a compound of formula I, wherein Cy₂ is 30 optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted heterocyclenyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted fused heteroaryl/heterocyclyl, optionally substituted fused heteroaryl/heterocyclenyl, optionally substituted fused heteroaryl/cycloalkenyl, optionally substituted fused heteroaryl/cycloalkyl, fused arylheterocyclyl, optionally substituted fused arylheterocyclenyl, or optionally substituted aryl.

Another preferred aspect of the invention is a compound of formula I, wherein Cy₂ is optionally substituted azaheteroaryl, optionally substituted azaheterocyclyl, optionally substituted azaheterocyclenyl, optionally substituted fused arylazaheteroclyl, optionally substituted fused arylazaheterocyclenyl, optionally substituted fused heteroarylazaheteroclyl, 5 optionally substituted fused heteroarylazaheterocyclenyl, optionally substituted fused azaheteroarylcy cloalkyl, optionally substituted fused azaheteroarylcy clokenyl, optionally substituted azaheterocyclyl, or optionally substituted heterocyclenyl.

Another preferred aspect of the invention is a compound of formula I, wherein Cy₂ is optionally substituted with one or more groups selected from amino, carbamoyl, acylamino, 10 heteroaryl, heterocyclenyl, heterocyclyl, alkyl, alkyloxycarbonyl, amidino, hydroxy, alkoxy, aryl, isourea, guanidino, acylhydrazino, acyl, cyano, carboxy, sulfamoyl, or halo.

Another preferred aspect of the invention is a compound of formula I, wherein Cy₂ is optionally substituted with one of more groups selected from aralkylamino, heteroaralkylamino, heterocyclalkylamino, heterocyclenylalkylamino, alkylcarbamate, aminoalkylamino, 15 aryloxycarbonylalkyl, heteroaryloxycarbonylalkyl, heterocycloxy carbonylalkyl, heterocyclenyoxy carbonylalkyl, and alkoxy carbonylalkyl.

Another preferred aspect of the invention is a compound of formula I, wherein Cy₂ optionally contains at least substituent selected from oxime and oxo when Cy₂ is cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, fused arylcycloalkyl, fused arylcycloalkenyl, fused 20 arylheterocyclyl, fused arylheterocyclenyl, fused heteroarylcy cloalkyl, fused heteroarylcy cloalkenyl, fused heteroarylheterocyclyl or fused heteroarylheterocyclenyl.

Another preferred aspect of the invention is a compound of formula I, wherein R₁, R_{1a}, R₂, R_{2a}, R₄, or R_{4a} are hydrogen.

Another preferred aspect of the invention is a compound of formula I, wherein R₄, and 25 R_{4a} taken together form O or S.

Another preferred aspect of the invention is a compound of formula I, wherein R₄, and R_{4a} taken together form O.

Another preferred aspect of the invention is a compound of formula I, wherein R₁, R_{1a}, R₂ and R_{2a} are hydrogen.

Another preferred aspect of the invention is a compound of formula I, wherein R₁, R_{1a}, R₄ and R_{4a} are hydrogen.

Another preferred aspect of the invention is a compound of formula I, wherein R₄ and R_{4a} are hydrogen.

Another preferred aspect of the invention is a compound of formula I, wherein R₄ is 35 optionally substituted lower alkyl.

Another preferred aspect of the invention is a compound of formula I, wherein R₄ is alkoxyalkyl, alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, alkoxy carbonylalkyl, hydroxyalkyl, acylalkyl, acylaminoalkyl or carbamoylalkyl.

Another preferred aspect of the invention is a compound of formula I, wherein R₂ is

5 optionally substituted lower alkyl.

Another preferred aspect of the invention is a compound of formula I, wherein R₂ and R_{2a} are hydrogen.

Another preferred aspect of the invention is a compound of formula I, wherein R₂ alkoxyalkyl, alkoxy carbonylalkyl, carboxyalkyl, hydroxyalkyl or heterocyclalkyloxycarbonyl, 10 and R_{2a} is hydrogen.

Another preferred aspect of the invention is a compound of formula I, wherein R₁ and R_{1a} are hydrogen.

Another preferred aspect of the invention is a compound of formula I, wherein R₁ is lower alkyl, carboxy, alkoxy carbonyl or carbamoyl, and R_{1a} is hydrogen.

15 Another preferred aspect of the invention is a compound of formula I, wherein R₁ is alkoxyalkyl, carboxyalkyl, alkoxy carbonylalkyl or carbamoylalkyl.

Another preferred aspect of the invention is a compound of formula I, wherein R₁ and R_{1a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group.

20 Another preferred aspect of the invention is a compound of formula I, wherein R₂ and R_{2a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group.

Another preferred aspect of the invention is a compound of formula I, wherein R₄ and R_{4a} taken together with the carbon atom through which they are linked form a 3 to 7 membered 25 cycloalkyl or cycloalkenyl group.

Another preferred aspect of the invention is a compound of formula I, wherein R_{1a} and R_{2a} are absent and R₁ and R₂ together with the carbon atoms through which R₁ and R₂ are linked form an aryl or heteroaryl group.

Another preferred aspect of the invention is a compound of formula I, wherein R₁ and R₂ 30 together with the carbon atoms through which R₁ and R₂ are linked form a cycloalkyl group, cycloalkenyl group, heterocycl group, or heterocyclenyl group.

Another preferred aspect of the invention is a compound of formula I, wherein R₁ and R₂ together with the carbon atoms through which R₁ and R₂ are linked form a cyclohexyl group.

Another preferred aspect of the invention is a compound of formula I, wherein R₁ and R₂ 35 together with the carbon atoms through which R₁ and R₂ are linked form a cyclohexenyl group.

Another preferred aspect of the invention is a compound of formula I, wherein L₁ is absent, optionally substituted alkylene, optionally substituted alkenylene, -C(O)NR₅-, -S(O)p-, -C(O)-, -C(O)Y-C(X)Y-, -C(O)O-, C(O)NR₅-S(O)p-, -C(O)-C(O)NR₅S(O)p-, -S(O)pNR₅-, -C(O)-alkylene-O-, -C(O)-alkenylene-O-, -S(O)p-alkenylene-, -S(O)p-alkylene-, -C(O)-alkylene-C(O)-, 5 -C(O)-alkylene-S(O)p-, -S(O)p-alkylene-C(O)-, -C(O)-alkylene, -C(O)-alkenylene-, -alkylene-C(O)NR₅-, or -C(O)CH(OH)-alkylene-.

Another preferred aspect of the invention is a compound of formula I, wherein L₁ is methylene, -C(O)-alkylene-O-, -C(O)-alkenylene-, -S(O)p-alkenylene-, -C(O)C(O)NR₅- or -S(O)p-.

10 Another preferred aspect of the invention is a compound of formula I, wherein Cy₁ is optionally substituted aryl, heteroaryl, optionally substituted heterocyclyl, optionally substituted heterocyclenyl, optionally substituted cycloalkyl, optionally substituted cycolalkenyl, optionally substituted fused arylcycloalkyl, optionally substituted fused arylcycloalkenyl, optionally substituted fused arylheterocyclyl, optionally substituted fused arylheterocyclenyl, optionally substituted fused heteroarylcyloalkyl, optionally substituted fused heteroarylcyloalkenyl, 15 optionally substituted fused heteroarylheterocyclyl or optionally substituted fused heteroarylheterocyclenyl.

Another preferred aspect of the invention is a compound of formula I, wherein Cy₁ is 20 optionally substituted aryl, heteroaryl, optionally substituted heterocyclyl, optionally substituted heterocyclenyl, optionally substituted cycloalkyl or optionally substituted cycolalkenyl.

Another preferred aspect of the invention is a compound of formula I, wherein Cy₁ is 25 optionally substituted with one of more groups selected from amino, halo, hydroxyl, aryl, heteroaryl, amidino, alkyl, acylamino, carbamoyl, cyano, alkoxy, nitro, carbamate, sulfamyl.

Another preferred aspect of the invention is a compound of formula I, wherein Cy₁ is 30 optionally substituted with one of more groups selected from -NH₂, chloro, carbamate or aminosulfamyl.

Another preferred aspect of the invention is a compound of formula I, wherein Cy₁ 35 optionally contains at least substituent selected from oxime and oxo when Cy₁ is cycloalky, cycloalkenyl, heterocyclyl, heterocyclenyl, fused arylcycloalkyl, fused arylcycloalkenyl, fused arylheterocyclyl, fused arylheterocyclenyl, fused heteroarylcyloalkyl fused heteroarylcyloalkenyl, fused heteroarylheterocyclyl or fused heteroarylheterocyclenyl.

Another preferred aspect of the invention is a compound of formula I, wherein R₁ is alkyl, hydrogen or alkoxy carbonyl.

Another preferred aspect of the invention is a compound of formula I, wherein R₁ is 40 alkoxycarbonylalkyl.

Another preferred aspect of the invention is a compound of formula I, wherein R₁ is alkyl, R₄ is alkyl, L₁ is -S(O)₂-, -S(O)₂-alkenylene- or -S(O)₂-alkylene- and Cy₁ is optionally substituted heteroaryl.

Another preferred aspect of the invention is a compound of formula I, wherein R₁, R_{1a},

5 R₄, and R_{4a}, are hydrogen, L₁ is -S(O)₂-, -S(O)₂-alkenylene- or -S(O)₂-alkylene-, and Cy₁ is optionally substituted aryl.

Another preferred aspect of the invention is a compound of formula I, wherein R₁, R_{1a},

R₄, and R_{4a}, are hydrogen, L₁ is -S(O)₂-, -S(O)₂-alkenylene- or -S(O)₂-alkylene-, and Cy₁ is optionally substituted heteroaryl.

10 Another preferred aspect of the invention is a compound of formula I, wherein R₁, R_{1a}, R₄, and R_{4a}, are hydrogen, L₁ is -S(O)₂-, -S(O)₂-alkenylene- or -S(O)₂-alkylene-, and Cy₁ is optionally substituted azaheteroaryl.

Another preferred aspect of the invention is a compound of formula I, wherein R₁, R_{1a},

R_{1a}, R₄, and R_{4a}, are hydrogen, L₁ is -S(O)₂-, -S(O)₂-alkenylene- or -S(O)₂-alkylene-, and Cy₁ is optionally substituted thiaheteroaryl.

Another preferred aspect of the invention is a compound of formula I, wherein R₁, R_{1a},

R_{1a}, R₄, and R_{4a}, are hydrogen, L₁ is -S(O)₂-, -S(O)₂-alkenylene- or -S(O)₂-alkylene-, and Cy₁ is optionally substituted benzothiophenyl.

Another preferred aspect of the invention is a compound of formula I, wherein R₁, R_{1a},

20 R_{1a}, R₄, and R_{4a}, are hydrogen, L₁ is -S(O)₂-, -S(O)₂-alkenylene or -S(O)₂-alkylene, and Cy₁ is optionally substituted indolyl.

Another preferred aspect of the invention is a compound of formula I, wherein R₁, R_{1a},

R_{1a}, R₄, and R_{4a}, are hydrogen, L₁ is -S(O)₂-, -S(O)₂-alkenylene or -S(O)₂-alkylene, and Cy₁ is optionally substituted benzimidazolyl.

25 Another preferred aspect of the invention is a compound of formula I, wherein R₁, R_{1a}, R_{1a}, R₄, and R_{4a}, are hydrogen, L₁ is -S(O)₂-, -S(O)₂-alkenylene or -S(O)₂-alkylene, and Cy₁ is optionally substituted thienyl.

Another preferred aspect of the invention is a compound of formula I, wherein R₁ is alkyl,

R₄ is alkyl, L₁ is -S(O)₂-, -S(O)₂-alkenylene or -S(O)₂-alkylene, L₂ is alkylene, Cy₁ is optionally substituted heteroaryl and Cy₂ is optionally substituted heteroaryl.

Another preferred aspect of the invention is a compound of formula I, wherein R₁, R_{1a},

R_{1a}, R₄, and R_{4a}, are hydrogen, L₁ is -S(O)₂-, -S(O)₂-alkenylene or -S(O)₂-alkylene, L₂ is alkylene, Cy₁ is optionally substituted heteroaryl, and Cy₂ is optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heteroaryl, 30

35 optionally substituted heterocycl or optionally substituted heterocyclenyl.

Another preferred aspect of the invention is a compound of formula I, wherein R₁, R_{1a}, R₄, and R_{4a}, are hydrogen, L₁ is -S(O)₂-, -S(O)₂-alkenylene or -S(O)₂-alkylene, L₂ is alkylene, Cy₁ is optionally substituted heteroaryl, and Cy₂ is optionally substituted heteroaryl.

Another preferred aspect of the invention is a compound of formula I, wherein R₁, R_{1a},

5 R_{1a}, R₄, and R_{4a}, are hydrogen, L₁ is -S(O)₂-, -S(O)₂-alkenylene or -S(O)₂-alkylene, L₂ is alkylene, Cy₁ is heteroaryl, and Cy₂ is optionally substituted azaindolyl, optionally substituted quinazolinyl or optionally substituted piperdinyl.

Another preferred aspect of the invention is a compound of formula I, wherein R₁, R_{1a},

R_{1a}, R₄, and R_{4a}, are hydrogen, L₁ is -S(O)₂-, -S(O)₂-alkenylene or -S(O)₂-alkylene, L₂ is alkylene,

10 Cy₁ is optionally substituted azaheteroaryl, and Cy₂ is optionally substituted azaheteroaryl.

Another preferred aspect of the invention is a compound of formula I, wherein R₁, R_{1a},

R_{1a}, R₄, and R_{4a}, are hydrogen, L₁ is -S(O)₂-, -S(O)₂-alkenylene or -S(O)₂-alkylene, L₂ is alkylene,

Cy₁ is optionally substituted thiaheteroaryl, and Cy₂ is optionally substituted azaindolyl,

optionally substituted quinazolinyl or optionally substituted piperdinyl.

15 Another preferred aspect of the invention is a compound of formula I, wherein R₁, R_{1a},

R_{1a}, R₄, and R_{4a}, are hydrogen, L₁ is -S(O)₂-, -S(O)₂-alkenylene or -S(O)₂-alkylene, L₂ is alkylene,

Cy₁ is optionally substituted benzothiophenyl, and Cy₂ is optionally substituted azaindolyl,

optionally substituted quinazolinyl or optionally substituted piperdinyl.

Another preferred aspect of the invention is a compound of formula I, wherein R₁, R_{1a},

20 R_{1a}, R₄, and R_{4a}, are hydrogen, L₁ is -S(O)₂-, -S(O)₂-alkenylene or -S(O)₂-alkylene, L₂ is alkylene,

Cy₁ is optionally substituted indolyl, and Cy₂ is optionally substituted azaindolyl, optionally

substituted quinazolinyl or optionally substituted piperdinyl.

Another preferred aspect of the invention is a compound of formula I, wherein R₁, R_{1a},

R_{1a}, R₄, and R_{4a}, are hydrogen, L₁ is -S(O)₂-, -S(O)₂-alkenylene or -S(O)₂-alkylene, L₂ is alkylene,

25 Cy₁ is optionally substituted benzimidazolyl, and Cy₂ is optionally substituted azaindolyl,

optionally substituted quinazolinyl or optionally substituted piperdinyl.

Another preferred aspect of the invention is a compound of formula I, wherein R₁, R_{1a},

R_{1a}, R₄, and R_{4a}, are hydrogen, L₁ is -S(O)₂-, -S(O)₂-alkenylene or -S(O)₂-alkylene, L₂ is alkylene,

Cy₁ is optionally substituted thienyl, and Cy₂ is optionally substituted azaindolyl or optionally

30 substituted quinazolinyl.

Another preferred aspect of the invention is a compound of formula I, wherein Cy₂ is quinazolinyl substituted by an amino substituent.

Another preferred aspect of the invention is a compound of formula I, wherein Cy₂ is quinazolinyl substituted by -NH₂ or -N(alkyl)₂.

Another preferred aspect of the invention is a compound of formula I, wherein R₂ is hydrogen, carboxyalkyl, alkoxyalkyl, hydroxyalkyl, alkoxycarbonylalkyl, acylamino or carbamoyl.

Another preferred aspect of the invention is a compound of formula I, wherein Cy₂ is piperdinyl.

5 Another preferred aspect of the invention is a compound of formula I, wherein Cy₂ is N-substituted piperdinyl.

Another preferred aspect of the invention is a compound of formula I, wherein Cy₂ is N-substituted piperdinyl and the piperdinyl moiety is attached to the parent moiety at the 4-position of the piperdinyl ring.

10 Another preferred aspect of the invention is a compound of formula I, wherein Cy₂ is a piperdinyl moiety substituted on the nitrogen ring atom by a group selected from aryl or heteroaryl.

Another preferred aspect of the invention is a compound of formula I, wherein Cy₂ is a piperdinyl moiety substituted on the nitrogen ring atom by an azaheteroaryl group.

15 Another preferred aspect of the invention is a compound of formula I, wherein Cy₂ is a piperdinyl moiety substituted on the nitrogen ring atom by a group selected from 2-pyridyl, 4-pyridyl or 4-pyrimidyl.

20 Another preferred aspect of the invention is a compound of formula I, wherein Cy₂ is a piperdinyl moiety substituted on the nitrogen ring atom by an optionally substituted pyrimidyl group.

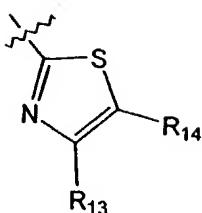
Another preferred aspect of the invention is a compound of formula I, wherein Cy₂ is a piperdinyl moiety substituted on the nitrogen ring atom by a pyrimidyl group wherein said pyrimidyl group is attached to the piperdinyl moiety at the 4-position of said pyrimidyl group.

25 Another preferred aspect of the invention is a compound of formula I, wherein Cy₂ is a piperdinyl moiety substituted on the nitrogen ring atom by a pyrimidyl group wherein said pyrimidyl group is substituted by an aryl group substituent, more preferably, said pyrimidyl group is substituted at its 2-position by a group selected from halogen, alkoxy, alkylthio and Y₁Y₂N-, wherein Y₁ and Y₂ are independently, hydrogen, alkyl or aralkyl.

30 Another preferred aspect of the invention is a compound of formula I, wherein Cy₂ is optionally substituted thiazolyl.

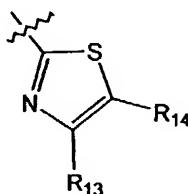
Another preferred aspect of the invention is a compound of formula I, wherein Cy₂ is thiazolyl substituted by at least one substituent selected from lower alkyl, aryl, heteroaryl, amino, acylaminoalkyl, alkoxycarbonylalkyl, carbamoylalkyl and alkoxyalkyl.

35 Another preferred aspect of the invention is a compound of formula I, wherein Cy₂ is a group of formula



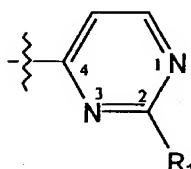
wherein R₁₃ and R₁₄ are independently hydrogen, lower alkyl, aryl, heteroaryl, amino, acylaminoalkyl, alkoxy carbonylalkyl, carbamoylalkyl or alkoxyalkyl; or R₁₃ and R₁₄ together with the carbon atoms through which R₁₃ and R₁₄ are linked form a cycloalkyl group, cycloalkenyl group, heterocycl group, heterocyclenyl group, aryl group or heteroaryl group.

5 Another preferred aspect of the invention is a compound of formula I, wherein Cy₂ is a group of formula



wherein R₁₃ and R₁₄ together with the carbon atoms through which R₁₃ and R₁₄ are linked form a cycloalkyl group, cycloalkenyl group, heterocycl group or heterocyclenyl group, optionally substituted with an oxo moiety.

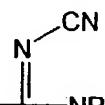
Another preferred aspect of the invention is a compound of formula I, wherein Cy₂ is a piperdinyl moiety substituted on the nitrogen ring atom by a pyrimidyl group of formula



15 R₁₅ wherein R₁₅ is selected from halogen, alkoxy, alkylthio and Y₁Y₂N-, wherein Y₁ and Y₂ are independently, hydrogen, alkyl and aralkyl.

Another preferred aspect of the invention is a compound of formula I, wherein Cy₂ is a piperdinyl moiety substituted on the nitrogen ring atom by a group selected from alkoxy carbonyl, carbamoyl, acyl, alkyl and amidino.

Another preferred aspect of the invention is a compound of formula I, wherein Cy₂ is a



20 piperdinyl moiety substituted on the nitrogen ring atom by —NR₁₂R₁₂' wherein R₁₂ and R₁₂' are independently selected from hydrogen or optionally substituted lower alkyl.

Other preferred compounds have formula I wherein m is 1; and n is 1.

Other preferred compounds have formula I wherein A is N.

Other preferred compounds have formula I wherein R₃ and R_{3a} taken together are O; and R₁, R_{1a}, R₂, R_{2a}, R₄ and R_{4a} are hydrogen.

5

Other preferred compounds have formula I wherein R₃ and R_{3a} taken together are O; R₁, R_{1a}, R₂, R_{2a} and R₄ are hydrogen; and R_{4a} is optionally substituted alkyl.

Other preferred compounds have formula I wherein R₃ and R_{3a} taken together are O; R₁,

10 R_{1a}, R₂ and R₄ are hydrogen; and R_{2a} and R_{4a} are optionally substituted alkyl.

Other preferred compounds have formula I wherein R₃ and R_{3a} taken together are O; R₁,

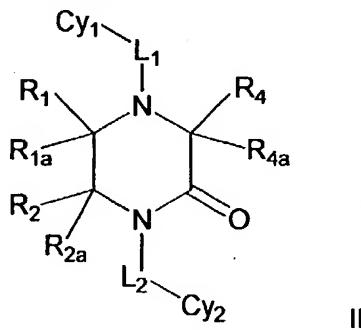
R₂, R_{2a} and R₄ are hydrogen; and R_{1a} and R_{4a} are optionally substituted alkyl.

15 Other preferred compounds have formula I wherein R₃ and R_{3a} taken together are O; R₁, R₂, R_{2a}, R₄ and R_{4a} are hydrogen; and R_{1a} is carboxy, alkoxy carbonyl, Y₁Y₂NCO or optionally substituted alkyl.

Other preferred compounds have formula I wherein R₃ and R_{3a} taken together are O;

20 and R₁, R_{1a}, R₂, R₄ and R_{4a} are hydrogen; and R_{2a} is carboxy, alkoxy carbonyl, Y₁Y₂NCO or optionally substituted alkyl.

Another preferred aspect of the invention is directed to a compound of formula II



or a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an

25 N-oxide thereof, a hydrate thereof or a solvate thereof,

wherein R₁, R_{1a}, R₂, R_{2a}, R₄, R_{4a}, Cy₂, L₁, and L₂ are as defined in formula I.

Preferred compounds have formula I or formula II wherein Cy₂ contains at least one nitrogen atom and when Cy₂ is optionally substituted aryl, optionally substituted cycloalkyl,

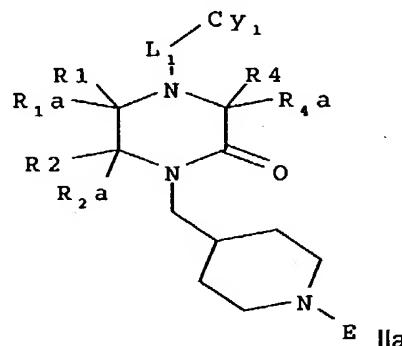
optionally substituted cycloalkenyl, optionally substituted fused phenylcycloalkyl or optionally substituted fused phenylcycloalkenyl, then said nitrogen atom is a basic nitrogen atom.

Another preferred aspect of the invention is a compound of formula I or formula II,

5 wherein Z is absent or is selected from O, S(O)_p and NR₅.

Another preferred aspect of the invention is a compound of formula I or formula II,
wherein Z is -NR₅C(O)- or -C(O)NR₅-.

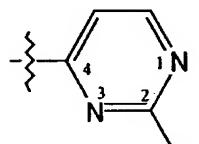
Another preferred aspect of the invention is a compound of formula IIa,



10

wherein R₁, R_{1a}, R₂, R_{2a}, R₃, R_{3a}, R₄, R_{4a}, Cy₁, and L₁, are as defined in formula I, E is

alkoxycarbonyl, carbamoyl, acyl, alkyl, pyridinyl, amidino; —NR₁₂R₁₂' wherein R₁₂ and R₁₂' are independently selected from hydrogen or optionally substituted lower alkyl; or



R₁₅ wherein R₁₅ is selected from halogen, alkoxy, alkylthio and Y₁Y₂N-, wherein

15 Y₁ and Y₂ are independently, hydrogen, alkyl and aralkyl.

Another preferred aspect of the invention is a compound of formula I or formula II,

wherein L₁ is -S(O)_p-, -C(X)Y- or -L₃-Q-L4-Q'-L5-.

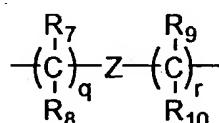
20 Another preferred aspect of the invention is a compound of formula I or formula II,
wherein Cy₁ is optionally substituted aryl or optionally substituted heteroaryl.

Another preferred aspect of the invention is a compound of formula I wherein R₁, R₂, R₃ and R₄ are independently alkyl, alkoxyalkyl, aminoalkyl, aminoalkylalkoxy, heterocyclyl, heterocyclenyl, heteroaryl, aryl, cycloalkyl, or cycloalkenyl or R₄ and R_{4a} taken together form O.

5 More preferred compounds are those having a structure of formula I or formula II, wherein L₂ is alkylene of one to three carbon atoms.

Other more preferred compounds are those having a structure of formula I or formula II, wherein L₂ is -CH₂-.

10 Other more preferred compounds are those having a structure of formula I or formula II, wherein L₂ is a group of formula



15 wherein Z is NR₅; q is 2; r is 0; R₅ is hydrogen or optionally substituted alkyl; and R₇ and R₈ are hydrogen.

Other more preferred compounds are those having a structure of formula I or formula II, wherein R₅ is hydrogen.

20 Other more preferred compounds are those having a structure of formula I or formula II, wherein Cy₂ is optionally substituted aryl or optionally substituted heteroaryl.

Other more preferred compounds are those having a structure of formula I or formula II, wherein L₁ is -S(O)₂-.

25 Other more preferred compounds are those having a structure of formula I or formula II, wherein L₁ is -C(X)Y-; X is O; and Y is NH.

Other more preferred compounds are those having a structure of formula I or formula II, 30 wherein L₁ is -L₃-Q-L₄-Q'-L₅-; Q is -S(O)₂- or -C(O)-; and L₄ is optionally substituted alkenylene.

Other more preferred compounds are those having a structure of formula I or formula II, wherein L₁ is -L₃-Q-L₄-Q'-L₅-; and L₄ is optionally substituted alkylene.

Other more preferred compounds are those having a structure of formula I or formula II, wherein L_1 is $-L_3-Q-L_4-Q'-L_5-$; Q is $-C(O)-$; Q' is O ; and L_4 is optionally substituted alkylene.

5 Other more preferred compounds are those having a structure of formula I or formula II, wherein L_1 is methylene, $-L_3-Q-L_4-Q'-L_5-$; L_3 is optionally substituted alkylene; and L_4 is optionally substituted alkenylene.

10 Other more preferred compounds are those having a structure of formula I or formula II, wherein Cy_1 is optionally substituted phenyl, optionally substituted thienyl, optionally substituted benzothienyl, optionally substituted isoquinolinyl, optionally substituted indolyl, optionally substituted thienopyridyl, optionally substituted furanyl, optionally substituted pyridyl, or optionally substituted benzimidazolyl.

15 Other more preferred compounds are those having a structure of formula I or formula II, wherein Cy_2 is optionally substituted phenyl, optionally substituted pyridyl, optionally substituted imidazolyl, optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted quinazolinyl, optionally substituted cinnolinyl, optionally substituted azaindolyl, or optionally substituted thienopyridyl.

20 Other more preferred compounds are those having a structure of formula I wherein A is N ;

G_1 is L_1-Cy_1 , and G_2 is L_2-Cy_2 ;

25 L_1 and L_2 are independently absent, methylene, ethylene, sulfonyl, alkylsulfonyl or alkylene; Cy_1 is thiaheteroaryl, thiaheterocyclyl, thiaheterocyclenyl, fused thiaheteroarylalkyl, fused thiaheteroarylalkenyl, fused heteroarylthiacycloalkyl or fused heteroarylthiacycloalkenyl, thiophen-isoxazolyl, thieno-pyridinyl, benzo-thiophen, indolyl, morpholinyl, aminopyridine-benzyl, pyrimidin-benzyl, aminoquinazolin, pyrimidin-piperidin, thiophen-pyrazol, thiophen-oxadiazol, thiophen-thiadiazol, thiophen-triazol, thiophen-pyridin, phenyl-triazol optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocyclyl, optionally substituted heterocyclenyl, optionally substituted fused arylcycloalkyl, optionally substituted fused arylcycloalkenyl, optionally substituted fused arylheterocyclyl, optionally substituted fused arylheterocyclenyl, optionally substituted fused heteroarylalkyl, optionally substituted fused

heteroarylcyloalkenyl, optionally substituted fused heteroarylheterocycl or optionally substituted fused heteroarylheterocyclenyl;

Cy₂ is amino-quinazolin, benzhydrylidene-amino, pyrrolo-pyridin, bipyridinyl, pyridin-benzyl, thiophenyl, thiophen-benzyl, optionally substituted aryl, optionally substituted heteroaryl,

5 optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocycl, optionally substituted heterocyclenyl, optionally substituted fused arylcycloalkyl, optionally substituted fused arylcycloalkenyl, optionally substituted fused arylheterocycl, optionally substituted fused arylheterocyclenyl, optionally substituted fused heteroarylcyloalkyl, optionally substituted fused heteroarylcyloalkenyl, optionally substituted fused

10 heteroarylheterocycl, optionally substituted fused heteroarylheterocyclenyl, azaheteroaryl, azaheterocycl, azaheterocyclenyl, fused azaheteroarylcyloalkyl, fused azaheteroarylcyloalkenyl, fused heteroarylazacycloalkyl or fused heteroarylazacycloalkenyl;

R₃ and R_{3a} taken together form O or S;

R₂ and R_{2a} are independently selected from hydrogen, alkyl, aminoalkyl, alkylaminoalkyl, alkoxy,

15 alkoxyalkyl, alkoxyaminoalkyl, cycloalkalkylamino, benzyloxyalkyl, isopropyl, aminomethyl, methoxyethylaminomethyl, piperazin, pyrrolidin, ethoxymethyl, benzyloxymethyl, methoxymethyl, isobutyl, isopropylamino or isopropylaminomethyl, provided that R₂ and R_{2a} are not each hydrogen, or carboxy, alkoxycarbonyl, Y₁Y₂NC(O)-, wherein Y₁ and Y₂ are defined as in formula I, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl,

20 optionally substituted heteroaryl and optionally substituted heteroaralkyl; or R₁ and R₂ together with the carbon atoms through which R₁ and R₂ are linked form a cycloalkyl group, cycloalkenyl group, heterocycl group, or heterocyclenyl group; or R_{1a} and R_{2a} are absent and R₁ and R₂ together with the carbon atoms through which R₁ and R₂ are linked form an aryl or heteroaryl group; or R₂ and R_{2a} taken together with the carbon atom through which they are linked form a 3

25 to 7 membered cycloalkyl or cycloalkenyl group;

R₁ and R_{1a} are independently selected from hydrogen, carboxy, alkoxycarbonyl, Y₁Y₂NC(O)-, wherein Y₁ and Y₂ are defined as in formula I, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl;

30 or R₁ and R_{1a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group;

R₄ and R_{4a} are independently selected from hydrogen, carboxy, alkoxycarbonyl, Y₁Y₂NC(O)-, wherein Y₁ and Y₂ are defined as in formula I, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted

35 heteroaralkyl or R₄ and R_{4a} taken together with the carbon atom through which they are linked

form a 3 to 7 membered cycloalkyl or cycloalkenyl group, or R₄ and R_{4a} taken together form O or S; and m and n are each 1.

Other more preferred compounds are those having a structure of formula I wherein A is

5 N;

G₁ is L₁-Cy₁ and G₂ is L₂-Cy₂;

L₁ is sulfonyl or alkylenesulfonyl;

L₂ is absent, methylene, ethylene or alkylene;

Cy₁ is thiaheteroaryl, thiaheterocyclyl, thiaheterocyclenyl, fused thiaheteroaryl cycloalkyl, fused
10 thiaheteroaryl cycloalkenyl, fused heteroarylthiacycloalkyl or fused heteroarylthiacycloalkenyl,
thiophen-isoxazolyl, thieno-pyridinyl, benzo-thiophen, indolyl, morpholinyl, optionally substituted
aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted
cycloalkenyl, optionally substituted heterocyclyl, optionally substituted heterocyclenyl, optionally
substituted fused arylcycloalkyl, optionally substituted fused arylcycloalkenyl, optionally
15 substituted fused arylheterocyclyl, optionally substituted fused arylheterocyclenyl, optionally
substituted fused heteroaryl cycloalkyl, optionally substituted fused heteroaryl cycloalkenyl,
optionally substituted fused heteroaryl heterocyclyl or optionally substituted fused
heteroaryl heterocyclenyl;

Cy₂ is amino-quinazolin, benzhydrylidene-amino, pyrrolo-pyridin, optionally substituted aryl,
20 optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted
cycloalkenyl, optionally substituted heterocyclyl, optionally substituted heterocyclenyl, optionally
substituted fused arylcycloalkyl, optionally substituted fused arylcycloalkenyl, optionally
substituted fused arylheterocyclyl, optionally substituted fused arylheterocyclenyl, optionally
substituted fused heteroaryl cycloalkyl, optionally substituted fused heteroaryl cycloalkenyl,
25 optionally substituted fused heteroaryl heterocyclyl, optionally substituted fused
heteroaryl heterocyclenyl, azaheteroaryl, azaheterocyclyl, azaheterocyclenyl, fused
azaheteroaryl cycloalkyl, fused azaheteroaryl cycloalkenyl, fused heteroarylazacycloalkyl or
fused heteroarylazacycloalkenyl;

R₃ and R_{3a} taken together form O or S;

30 R₂ and R_{2a} are independently selected from hydrogen, alkyl, aminoalkyl, alkylaminoalkyl, alkoxy,
alkoxyalkyl, alkoxyaminoalkyl, cycloalkylalkylamino, benzyloxyalkyl, isopropyl, aminomethyl,
methoxyethylaminomethyl, piperazin, pyrrolidin, ethoxymethyl, benzyloxymethyl,
methoxymethyl, isobutyl, isopropylamino or isopropylaminomethyl, provided that R₂ and R_{2a} are
not each hydrogen;

R₁, R_{1a}, R₄ and R_{4a} are independently selected from hydrogen, carboxy, alkoxycarbonyl, Y₁Y₂NC(O)-, wherein Y₁ and Y₂ are defined as in claim 1, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl;

5 or the pairs R₁ and R_{1a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; or R₄ and R_{4a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group;

and m and n are each 1.

10

Other more preferred compounds are those having a structure of formula I wherein A is

N;

G₁ is L₁-Cy₁ and G₂ is L₂-Cy₂;

L₁ and L₂ are independently absent, methylene, ethylene or alkylene;

15 Cy₁ is thiophen-isoxazolyl, aminopyridine-benzyl, benzo-thiophen, pyrimidin-benzyl, aminoquinazolin, pyrimidin-piperidin, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted heterocycl, optionally substituted heterocyclenyl, optionally substituted fused arylcycloalkyl, optionally substituted fused arylcycloalkenyl, optionally substituted fused

20 arylheterocycl, optionally substituted fused arylheterocyclenyl, optionally substituted fused heteroarylcyloalkyl, optionally substituted fused heteroarylcyloalkenyl, optionally substituted fused heteroarylheterocycl or optionally substituted fused heteroarylheterocyclenyl;

Cy₂ is bipyridinyl, amino-quinazolin, pyridin-benzyl, thiophenyl, thiophen-benzyl, pyrrolo-pyridin, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl,

25 optionally substituted cycloalkenyl, optionally substituted heterocycl, optionally substituted heterocyclenyl, optionally substituted fused arylcycloalkyl, optionally substituted fused arylcycloalkenyl, optionally substituted fused arylheterocycl, optionally substituted fused heteroarylcyloalkyl, optionally substituted fused heteroarylcyloalkenyl, optionally substituted fused heteroarylheterocycl, optionally substituted fused heteroarylheterocyclenyl or optionally

30 substituted fused heteroarylheterocyclenyl;

R₃ and R_{3a} taken together form O or S; and

R₄ and R_{4a} taken together form O or S;

R₁, R_{1a}, R₂, R_{2a}, are independently selected from hydrogen, carboxy, alkoxycarbonyl,

Y₁Y₂NC(O)-, wherein Y₁ and Y₂ are defined as in claim 1, optionally substituted alkyl, optionally

35 substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally

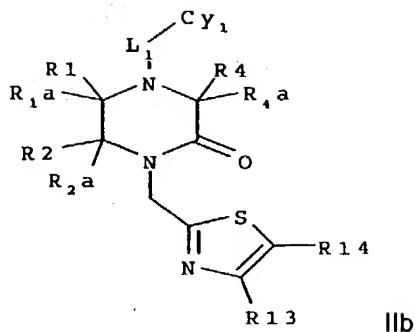
substituted heteroaralkyl; or R₁ and R₂ together with the carbon atoms through which R₁ and R₂ are linked form a cycloalkyl group, cycloalkenyl group, heterocyclyl group, or heterocyclenyl group; or R_{1a} and R_{2a} are absent and R₁ and R₂ together with the carbon atoms through which R₁ and R₂ are linked form an aryl or heteroaryl group; or one or more of the pairs R₁ and R_{1a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; or R₂ and R_{2a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group;

5 and m and n are each 1.

10 Other more preferred compounds are those having a structure of formula I wherein A is N; G₁ is L₁-Cy₁ and G₂ is L₂-Cy₂; L₁ and L₂ are independently absent, methylene, ethylene or alkylene; Cy₁ is thiophen-isoxazol, thiophen-pyrazol, thiophen-oxadiazol, thiophen-thiadiazol, thiophen-triazol, thiophen-pyridin or phenyl-triazol;

15 Cy₂ is amino-quinazolin or pyrrolo-pyridin; R₃ and R_{3a} taken together form O or S; R₁, R_{1a}, R₂, R_{2a}, R₄ and R_{4a} are independently selected from hydrogen, carboxy, alkoxy carbonyl, Y₁Y₂NC(O)-, wherein Y₁ and Y₂ are defined as in claim 1; optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl; or R₁ and R₂ together with the carbon atoms through which R₁ and R₂ are linked form a cycloalkyl group, cycloalkenyl group, heterocyclyl group, or heterocyclenyl group; or R_{1a} and R_{2a} are absent and R₁ and R₂ together with the carbon atoms through which R₁ and R₂ are linked form an aryl or heteroaryl group; or one or more of the pairs R₁ and R_{1a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; or R₂ and R_{2a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; or R₄ and R_{4a} taken together with the carbon atom through which they are linked form a 3 to 7 membered cycloalkyl or cycloalkenyl group; and m and n are each 1.

25 Another preferred aspect of the invention is a compound of formula IIb



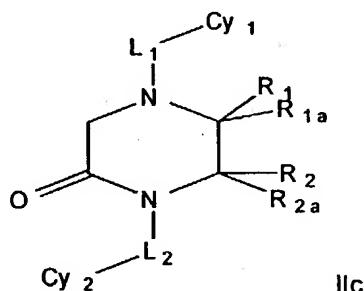
IIb

or a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof,
wherein L₁, Cy₁, R₁, R_{1a}, R₂, R_{2a}, R₄ and R_{4a} are as described in compound of formula I,

5 R₁₃ and R₁₄ are independently hydrogen, lower alkyl, aryl, heteroaryl, amino, acylaminoalkyl, alkoxy carbonylalkyl, carbamoylalkyl or alkoxyalkyl; or R₁₃ and R₁₄ together with the carbon atoms through which R₁₃ and R₁₄ are linked form a cycloalkyl group, cycloalkenyl group, heterocycl group, heterocyclenyl group, aryl group or heteroaryl group.

Another preferred aspect of the invention is a compound of formula IIb wherein R₁₃ and
10 R₁₄ together with the carbon atoms through which R₁₃ and R₁₄ are linked form a cycloalkyl group, cycloalkenyl group, heterocycl group or heterocyclenyl group, optionally substituted with an oxo moiety.

Other preferred compounds are those which inhibit both Factor Xa and Factor IIa (thrombin) activity, having a structure of formula IIc



IIc

15

or a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof, wherein:
Cy₁ is thiaheteroaryl, benzothiophenyl or azaheteroaryl, which are unsubstituted or substituted by halogen,
20 L₁ is -S(O)₂-, -S(O)₂-alkylene-, -S(O)₂-alkyenylene- or -S(O)₂-alkynylene-;
R₁, R_{1a}, R₂, R_{2a} are independently hydrogen, alkyl, alkoxyalkyl, aminoalkyl, aminoalkylalkoxy, carboxyl, alkoxy carbonyl, or carbamoyl; L₂ is methylene; and

Cy₂ is azaheteroaryl, azaheterocyclyl, azaheterocyclenyl, fused azaheteroarylcy cloalkyl, fused azaheteroarylcy cloalkenyl, fused heteroarylazacycloalkyl or fused heteroarylazacycloalkenyl.

Other preferred compounds which inhibit both Factor Xa and Factor IIa (thrombin)

5 activity are those having a structure of formula IIc wherein:

Cy₁ is thiaheteroaryl or azaheteroaryl,

L₁ is -S(O)₂-, -S(O)₂-alkylene-, -S(O)₂-alkylenene- or -S(O)₂-alkynylene-;

R₁, R_{1a}, R₂, R_{2a} are independently hydrogen, alkoxyalkyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, carboxyl, alkoxy carbonyl, or carbamoyl;

10 L₂ is methylene; and

Cy₂ is azaheteroaryl, azaheterocyclyl, azaheterocyclenyl, fused azaheteroarylcy cloalkyl, fused azaheteroarylcy cloalkenyl, fused heteroarylazacycloalkyl or fused heteroarylazacycloalkenyl.

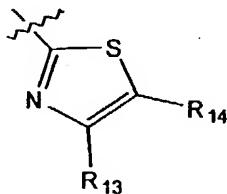
Other preferred compounds which inhibit both Factor Xa and Factor IIa (thrombin)

15 activity are those having a structure of formula IIc wherein Cy₂ is optionally substituted azaindolyl, optionally substituted quinazolinyl or optionally substituted piperdanyl.

Other preferred compounds which inhibit both Factor Xa and Factor IIa (thrombin) activity are those having a structure of formula IIc wherein R₁, R_{1a}, R₂, and R_{2a} are independently aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocyclyl or heterocyclenyl.

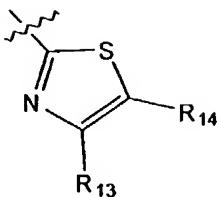
20 Other preferred compounds which inhibit both Factor Xa and Factor IIa (thrombin) activity are those having a structure of formula IIc wherein Cy₂ is an optionally substituted thiazolyl.

Other preferred compounds which inhibit both Factor Xa and Factor IIa (thrombin) activity are those having a structure of formula IIc wherein Cy₂ is a group of formula



25 wherein R₁₃ and R₁₄ are independently hydrogen, lower alkyl, aryl, heteroaryl, amino, acylaminoalkyl, alkoxy carbonylalkyl, carbamoylalkyl or alkoxyalkyl; or R₁₃ and R₁₄ together with the carbon atoms through which R₁₃ and R₁₄ are linked form a cycloalkyl group, cycloalkenyl group, heterocyclyl group, heterocyclenyl group, aryl group or heteroaryl group.

30 Other preferred compounds which inhibit both Factor Xa and Factor IIa (thrombin) activity are those having a structure of formula IIc wherein Cy₂ is a group of formula



wherein R₁₃ and R₁₄ together with the carbon atoms through which R₁₃ and R₁₄ are linked form a cycloalkyl group, cycloalkenyl group, heterocyclyl group or heterocyclenyl group, optionally substituted with an oxo or oxime substituent.

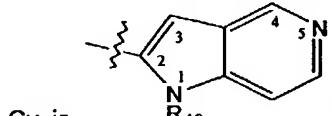
5 Other preferred compounds which inhibit both Factor Xa and Factor IIa (thrombin) activity are those having a structure of formula IIc wherein Cy₂ is optionally substituted azaindolyl.

More preferred compounds which inhibit both Factor Xa and Factor IIa (thrombin) activity are those having a structure of formula IIc wherein Cy₂ is optionally substituted 5-10 azaindolyl.

More preferred compounds which inhibit both Factor Xa and Factor IIa (thrombin) activity are those having a structure of formula IIc wherein,

when Cy₂ is optionally substituted azaindolyl, the parent molecule is attached to the azaindolyl group at the 2-position.

15 More preferred compounds which inhibit both Factor Xa and Factor IIa (thrombin) activity are those having a structure of formula IIc wherein



Cy₂ is wherein R₁₉ is hydrogen or optionally substituted alkyl.

More preferred compounds which inhibit both Factor Xa and Factor IIa (thrombin) activity are those having a structure of formula IIc wherein

20 Cy₂ is optionally substituted azaindolyl;

L₁ is -S(O)₂, -S(O)₂-alkenylene;

Cy₁ is optionally substituted thienyl or optionally substituted benzothiophenyl,

R₁ and R₂ are hydrogen;

R_{1a} and R_{2a} are independently hydrogen, alkyl, carboxyl, alkoxy carbonyl, or carbamoyl.

25 More preferred compounds which inhibit both Factor Xa and Factor IIa (thrombin)

activity are those having a structure of formula IIc wherein

R₁, R_{1a} and R₂ are hydrogen; and

R_{2a} is alkyl, carboxyl, alkoxy carbonyl, or carbamoyl.

More preferred compounds which inhibit both Factor Xa and Factor IIa (thrombin) activity are those having a structure of formula IIc wherein

Cy₂ is optionally substituted azaindolyl;

L₁ is -S(O)₂- or -S(O)₂-alkenylene;

5 Cy₁ is optionally substituted thieryl or optionally substituted benzothiophenyl, optionally substituted, optionally substituted benzimidazolyl, or optionally substituted indolyl,

R₁, R_{1a} and R₂ are hydrogen; and

R_{2a} is alkyl, carboxyl, alkoxy carbonyl, or carbamoyl.

More preferred compounds which inhibit both Factor Xa and Factor IIa (thrombin)

10 activity are those having a structure of formula IIc wherein

R₁, R₂ and R_{2a} are hydrogen; and

R_{1a} is alkyl, carboxyl, alkoxy carbonyl, or carbamoyl.

More preferred compounds which inhibit both Factor Xa and Factor IIa (thrombin)

activity are those having a structure of formula IIc wherein

15 Cy₂ is optionally substituted azaindolyl;

L₁ is -S(O)₂- or -S(O)₂-alkenylene;

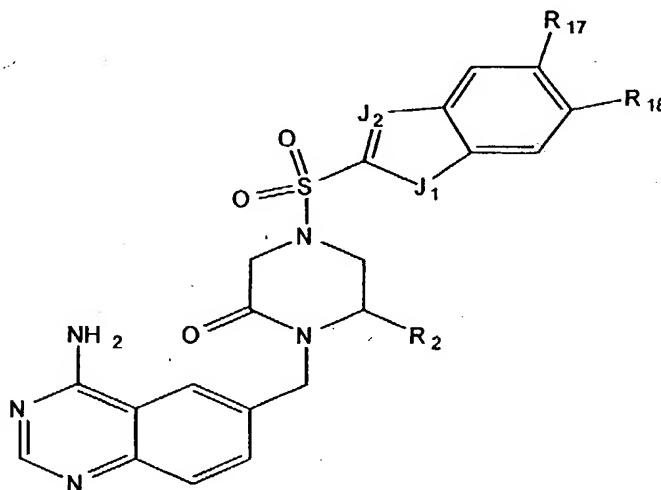
Cy₁ is optionally substituted thieryl or optionally substituted benzothiophenyl,

R_{1a} is alkyl, carboxyl, alkoxy carbonyl, or carbamoyl; and

R₁, R₂ and R_{2a} are hydrogen.

20 Other preferred compounds which inhibit both Factor Xa and Factor IIa (thrombin)

activity are those having a structure of formula IIId



IIId

wherein R₁₇ and R₁₈ are independently hydrogen or halogen;

J₁ is S or NH;

25 J₂ is CH or N; and

R₂ is hydrogen, alkyl, carboxyl, alkoxy carbonyl, or carbamoyl.

Another preferred aspect of the invention is a compound of formula II'd wherein R₂ is heterocyclalkyloxycarbonyl, heterocyclenylalkyloxycarbonyl, heteroaralkyloxycarbonyl, arylalkyloxycarbonyl, cycloalkylalkyloxycarbonyl, or cycloalkenylalkyloxycarbonyl.

5 Another preferred aspect of the invention is a compound of formula II'd wherein R₂ is heterocyclalkylcarbamoyl, heterocyclenylalkylcarbamoyl, heteroaralkylcarbamoyl, arylalkylcarbamoyl, cycloalkylcarbamoyl, or cycloalkenylcarbamoyl.

Another preferred aspect of the invention is a compound of formula II'd wherein R₂ is heterocyclyl, heterocyclenyl, heteroaryl, aryl, cycloalkyl, or cycloalkenyl.

10 Another preferred aspect of the invention is a compound of formula II'd wherein R₂ is heterocyclalkyloxycarbonylalkyl, heterocyclenylalkyloxycarbonylalkyl, heteroaralkyloxycarbonylalkyl, arylalkyloxycarbonylalkyl, cycloalkylalkyloxycarbonylalkyl, or cycloalkenylalkyloxycarbonylalkyl.

Another preferred aspect of the invention is a compound of formula II'd wherein R₂ is 15 heterocyclalkylcarbamoylalkyl, heterocyclenylalkylcarbamoylalkyl, heteroaralkylcarbamoylalkyl, arylalkylcarbamoylalkyl, cycloalkylcarbamoylalkyl, or cycloalkenylcarbamoylalkyl.

Another preferred aspect of the invention is a compound of formula II'd wherein R₂ is alkoxyalkyl, hydroxyalkyl or aminoalkyl.

20 Another preferred aspect of the invention is a compound of formula II'd wherein R₂ is alkyl(H)N-alkyl-.

Compounds contemplated as falling within the scope of this invention, include, but are not limited to

25

Preferred compounds wherein Z is -NR₅C(O)- or -C(O)NR₅- are selected from

or a pharmaceutically acceptable salt thereof, pharmaceutically acceptable prodrug thereof, an N-oxide thereof, a hydrate thereof or a solvate thereof.

30

Preferred intermediates according to this invention have formula III wherein Cy₂ contains at least one nitrogen atom and when Cy₂ is optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted fused phenylcycloalkyl or optionally substituted fused phenylcycloalkenyl, then said nitrogen atom is a basic nitrogen atom.

35

Other preferred intermediates according to this invention have formula III wherein Z is absent.

5 Other preferred intermediates according to this invention have formula III wherein R₁, R_{1a}, R₂, R_{2a}, R₄ and R_{4a} are hydrogen.

Other preferred intermediates according to this invention have formula II, wherein L₁ and L₂ independently are methylene, ethylene, propylene or butenylene; R₁, R_{1a}, R₂, R_{2a} are independently hydrogen, alkyl, alkoxyalkyl, aminoalkyl, aminoalkylalkoxy, carboxyl, alkoxycarbonyl, or carbamoyl; Cy₁ is heteroaryl, thiaheteroaryl, biheteroaryl, thiophenyl, isoxazolyl, isoxazolyl-thiophenyl or azaheteroaryl, which are unsubstituted or substituted by halogen; Cy₂ is azaheteroaryl, quinazolin, amino-quinazolin or 4-aminoquinazolin.

15 More preferred intermediates according to this invention are selected from (2S, 6RS)-4-(4-chloro-quinolin-7-ylmethyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester,
(3S,5RS)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one,
(3S, 5R)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one,
20 (3S, 5S)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one,
(3S, 5R)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one,
(2S, 6R)-4-(4-chloro-quinolin-7-ylmethyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester,
(3S, 5S)-1-(4-chloro-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,5-dimethyl-
25 piperazine-2-one,
(3S, 5R)-1-(4-chloro-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,5-dimethyl-
piperazine-2-one,
4-(2-Oxopiperazin-1-ylmethyl)benzamidine,
1-(2-Aminoquinolin-6-ylmethyl)piperazin-2-one,
30 1-(1-Aminoisoquinolin-6-ylmethyl)piperazin-2-one,
2-(2-Oxopiperazin-1-ylmethyl)pyrrolo[3,2-c]pyridin-1-carboxylic acid tert-butyl ester,
2-(5-(±)-Methoxycarbonyl-2-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid
tert-butyl ester,
2-(2-(±)-Methoxycarbonyl-6-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid
35 tert-butyl ester,

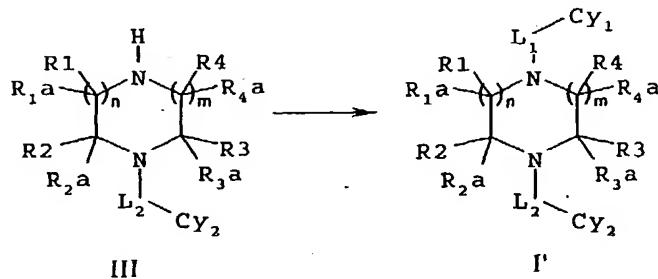
1-(4-Aminoquinazoline-7-ylmethyl)piperazine-2-one,
1-(4-Amino-thieno[2,3-d]pyrimidin-6-ylmethyl)-piperazin-2-one,
4-[3-(2-Oxo-piperazin-1-yl)-propyl]-piperidine-1-carboxylic acid tert-butyl ester,
1-(4-Amino-quinazoline-7-ylmethyl)-3-methoxymethyl-piperazine-2-one,
5 1-(4-Aminoquinazoline-7-ylmethyl)-3-butyl-piperazine-2-one,
1-(4-Aminoquinazoline-7-ylmethyl)-3-ethyl-piperazine-2-one,
1-(4-Aminoquinazoline-7-ylmethyl)-3-propyl-piperazine-2-one,
1-(4-Amino-quinazoline-7-ylmethyl)-3-ethoxymethyl-piperazine-2-one,
1-(4-Amino-quinazoline-7-ylmethyl)-3-methyl-piperazine-2-one,
10 1-(4-Amino-quinazoline-7-ylmethyl)-3-benzyl-piperazine-2-one,
1-(4-Amino-quinazoline-7-ylmethyl)-3-(1-methoxyethyl)-piperazine-2-one,
1-(4-Amino-quinazoline-7-ylmethyl)-3,3-dimethyl-piperazine-2-one,
1-(4-Amino-quinazoline-7-ylmethyl)-3-isopropyl-piperazine-2-one,
1-(4-Amino-quinazoline-7-ylmethyl)-3-isobutyl-piperazine-2-one,
15 1-(4-Amino-quinazoline-7-ylmethyl)-3-(2-methoxyethyl) 1-piperazine-2-one,
1-(4-Amino-quinazoline-7-ylmethyl)-3-methoxymethyl-6-methyl-piperazine-2-one,
(3S,5RS)-1-(4-amino-quinazolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one,
1-(4-Chloroquinolin-7-ylmethyl)-piperazin-2-one,
1-(4-Chlorocinnolin-7-ylmethyl)-piperazin-2-one,
20 1-(4-Chloroquinolin-7-ylmethyl)-3-(S)-methylpiperazin-2-one,
1-[2-(Pyridin-4-ylamino)-ethyl]-piperazin-2-one,
1-[2-((Methyl)-(pyridin-4-yl)-amino)-ethyl]-piperazin-2-one trifluoroacetate,
1-[2-(3-Methylpyridin-4-yl-amino)-ethyl]-piperazin-2-one,
1-[2-(Pyridazin-4-ylamino)-ethyl]-piperazin-2-one,
25 4-[3-(4-tert-Butoxycarbonylamino-pyridin-3-yl)-propenyl]-3-oxo-piperazine-1-carboxylic acid
tert-butyl ester,
4-[3-(4-tert-butoxycarbonylamino-pyridin-3-yl)-allyl]-3-oxo-piperazine-1-carboxylic acid tert-butyl
ester
4-[3-(4-tert-Butoxycarbonylamino-pyridin-3-yl)-propyl]-3-oxo-piperazine-1-carboxylic acid tert-
30 butyl ester.
4-(Benzylloxycarbonyl)-1-(2-pyrrolo[3,2-c]pyridin-1-ylethyl)-piperazin-2-one,
(\pm)-1-(3-Amino-4-cyano-benzyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-
carboxylic acid methyl ester and
(\pm)-1-(3-Amino-4-cyano-benzyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-
35 carboxylic acid.

Preparation of the Compounds of the Invention

A general route to the compounds of this invention wherein A is N and R₁, R_{1a}, R₂, R_{2a}, R₃, R_{3a}, R₄, R_{4a}, L₁, L₂, Cy₁, Cy₂, m and n are defined for Formula I above is outlined in Scheme

5 1.

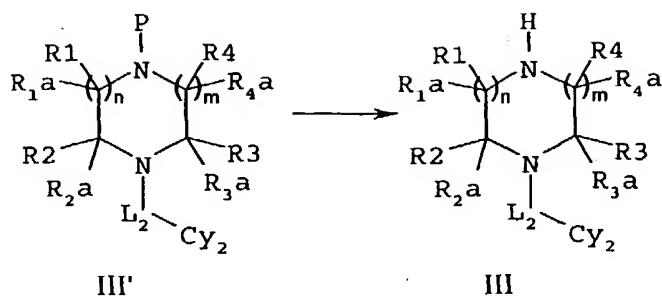
Scheme 1



As outlined in Scheme 1, coupling of a compound of formula III with a sulfonyl chloride, an alkyl halide, an acid or an activated derivative thereof, such as an acid anhydride or acid chloride, an isocyanate, chloroformate or activated sulfamoyl ester in an appropriate solvent, generates the compound of formula I in which the L₁-Cy₁ portion is a sulfonamide, alkyl amine, amide, urea, carbamate or sulfamyl urea, respectively. Sulfonamide formation is accomplished with a base such as a trialkylamine in an inert solvent such as dichloromethane, THF or acetonitrile at about 0 °C to about 100 °C in the presence or absence of an activating agent such as dimethylaminopyridine (DMAP). Alkyl amine formation can be achieved with a suitable base such as K₂CO₃ or trialkylamine in an appropriate solvent such as DMF or acetonitrile at about 0 °C to about 100 °C. Amide, urea, carbamate and sulfamyl urea formation can be conducted with acids and coupling reagents such as EDC or TBTU or with any variant of reactive acid derivatives and the use of an appropriate base additive such as triethylamine, N-methylmorpholine or diisopropylethylamine.

The preparation of a compound of formula III wherein R_1 , R_{1a} , R_2 , R_{2a} , R_3 , R_{3a} , R_4 , R_{4a} , L_2 , Cy_2 , m and n are as defined herein from formula 1, is outlined in Scheme 2.

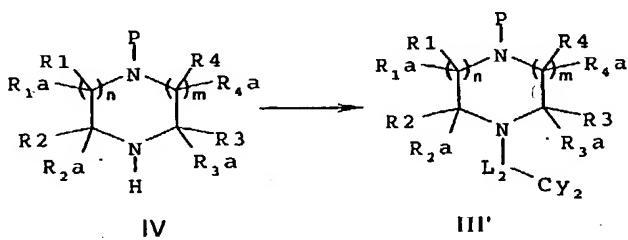
Scheme 2



As outlined in Scheme 2, a compound of formula III is prepared by removing a nitrogen protecting group P from the compound of formula III'. In a preferred aspect, P is an alkyl, aralkyl or aryl carbamate moiety, which is removed using strong acid, strong base or catalytic 5 hydrogenation in an appropriate solvent such as methanol or ethanol.

The preparation of a compound of formula III' wherein R₁, R_{1a}, R₂, R_{2a}, R₃, R_{3a}, R₄, R_{4a}, L₁, L₂, Cy₁, Cy₂, m and n and P are defined herein is outlined in Scheme 3.

Scheme 3

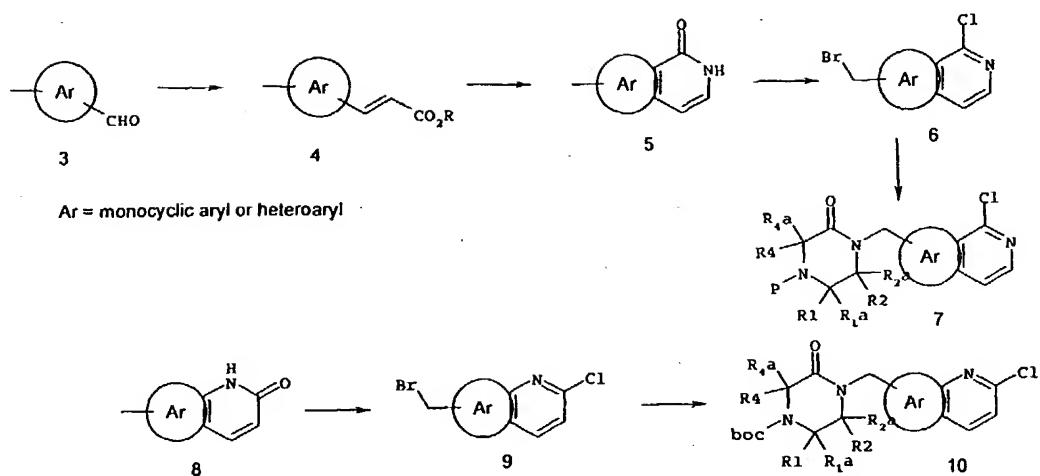


As indicated in Scheme 3, the compound of formula III' is obtained by coupling a compound of formula IV with an appropriate Cy₂-L₂-LG compound wherein LG is a leaving group, such as chloro, bromo, iodo, or optionally substituted lower alkylsulfonyloxy or 15 arylsulfonyloxy, in an inert organic solvent, such as THF, Et₂O or DMF, in the presence of a strong base such as NaH, lithium hexamethyldisilylazide or lithium diisopropylamine. In a preferred aspect, P is an alkyl, aralkyl or aryl carbamate group.

The preparation of intermediate compounds of formula 7 and 10 is outlined in Scheme

4.

20 Scheme 4



As indicated in Scheme 4, reacting a compound of formula 3 with an appropriate

malonic acid in a polar, such as pyridine or ethanol, and a base, such as piperidine or pyridine, at reflux provides a compound of formula 4 wherein R is H. Alternatively, a compound of

5 formula 3 may be reacted with a suitable Wittig or Horner-Emmons reagent in an inert solvent such as THF to give a compound of formula 4 wherein R is lower alkyl. When R is lower alkyl, the ester is hydrolyzed to the corresponding carboxylic acid (R is H) using an appropriate strong acid or alkali base. The corresponding acid is converted to the acid chloride using standard reagents such as thionyl chloride, or is converted to the mixed anhydride in a polar 10 solvent, such as acetone or THF, to form an activated acyl compound. The activated acyl compound is then treated with a solution of NaN_3 in water at about -10°C to about 25°C to yield the corresponding acyl azide. The acyl azide compound is then heated slowly in an inert solvent such as benzene or toluene at about 60°C to about 110°C and then concentrated in vacuo and heated in a higher boiling inert solvent, such as 1,2-dichlorobenzene or phenyl ether, 15 at about 180°C to about 240°C with a catalyst such as iodine or tributylamine to obtain a compound of formula 5. Alternatively the acyl azide compound can be added directly to a high boiling inert solvent, such as phenyl ether, at about 180°C to about 240°C with a catalyst such as iodine or tributylamine to obtain the compound of formula 5.

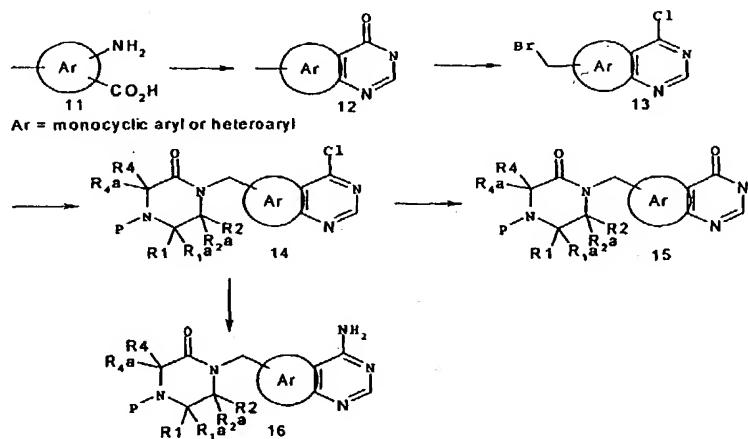
A compound of formula 8, prepared as described in Syn., 739 (1975), the contents of

20 which are hereby incorporated herein by reference, or a compound of formula 5 above, may be chlorinated using standard reagents such as POCl_3 or $\text{POCl}_3/\text{PCl}_5$ and halogenated using standard conditions, such as N-halosuccinimide and benzoyl peroxide in an inert solvent such as carbon tetrachloride, to give the corresponding chloro-halomethyl compounds 6 and 9, respectively. Compounds of formula 6 or 9 are coupled to compounds of formula IV, in which

R3 and R3a taken together form oxo, under basic condition employing NaH, or KOtBu or some other deprotonating base, to give compounds of formula 7 or 10.

The preparation of aminoquinazoline, quinazolinone or amino-thienopyrimidine intermediates is outlined in Scheme 5.

5 Scheme 5



As shown in Scheme 5, an aminoheteroaryl carboxylic acid or an aminoarylcarboxylic acid of formula 11, in which the amino and carboxylic acid are ortho to each other, is treated with formamidine under heat to form the corresponding quinazolinone or thienopyrimidinone 12.

10 The quinazolinone or thienopyrimidinone 12 is then converted to the chloroquinazoline or chlorothienopyrimidine using a chlorinating reagent such as $P(O)Cl_3$ and heat. The chloroquinazoline or chlorothienopyrimidine is brominated at the benzylic carbon using radical bromination conditions. Alternatively, a chloroquinazoline or chlorothienopyrimidine, containing a hydroxy-methylene group is converted to the corresponding bromide using CBr_4/PPh_3 ; or PBr_3 . The bromide 13 is then reacted with the anion of the ring nitrogen of a compound of formula III, formed using NaH , $LiN(SiMe_3)_3$, $NaN(SiMe_3)_3$, LDA, lithium alkoxide, sodium alkoxide or an appropriate base, in an inert solvent such as THF, DMF, ether, or DME. This yields compounds of formula 14 which contain a chloro-quinazoline or a chloro-thienopyrimidine group. The chloro group is converted to an amino group using NH_3 in ethanol in the presence of a catalytic amount of acid, such as HOAc to give compounds of formula 16. Alternatively, the chloro group is converted to a substituted amino group using a primary or secondary amine in an inert solvent. Alternatively, the chloro group is converted to a hydroxy group using acetic acid in water with heating or using a hydroxide source to give compounds of formula 15. Alternatively, the chloro is converted to an alkoxy group using an alcoholic solvent with heated

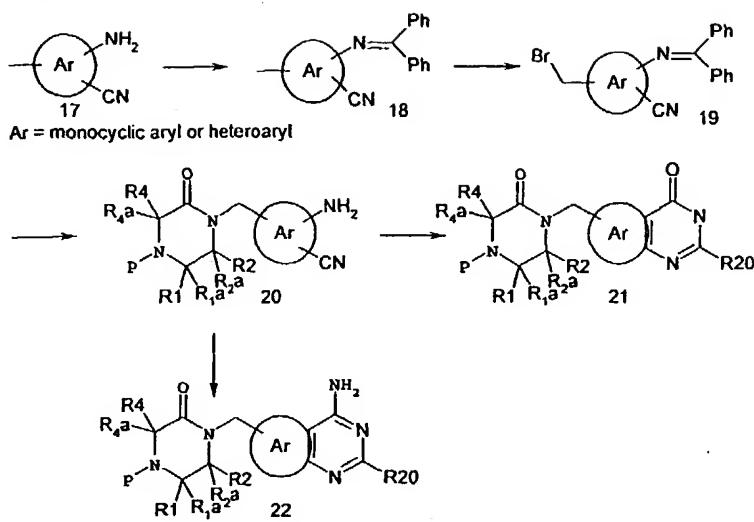
15 in the presence of a base.

20

25

An alternative synthesis of quinazolines and thienoquinazolines is outlined in Scheme 6.

Scheme 6.



As shown in Scheme 6, an amino-aryl nitrile or an amino heteroaryl nitrile 17 is treated with an aldehyde or ketone under imine forming conditions. The corresponding aryl or

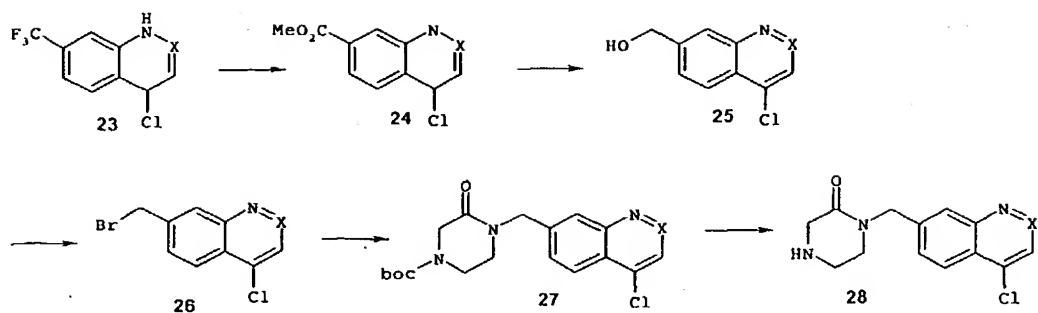
5 heteroaryl imine is brominated using radical bromination with NBS. The bromide is then coupled with compounds of formula IV under basic conditions, such as NaH, LiN(SiMe₃)₃, NaN(SiMe₃)₃, LDA, lithium alkoxides, sodium alkoxides or an appropriate base, in an inert solvent, such as THF, DMF, ether, or DME. This yields compounds of formula 20 in which



10 is an imino-aryl nitrile or an imino heteroaryl nitrile. The imine is deprotected using an acid such as HCl to give the corresponding aniline. The aniline-aryl-nitrile or the aniline-heteroaryl nitrile 20, is converted to the amino-quinazoline or thienopyrimidine, formula 22 (in which R₂₀=H), using triazine or formamidine. The quinazolinone or thienopyrimidinone, formula 21, in which R₂₀=H, is formed from a compound of formula 20 using formamide. Alternatively, compounds of formula 20 can be reacted under acid conditions, such as HCl (gas) in a solvent 15 such as ethanol in the presence of a nitrile, to give compounds of formula 22 in which R₂₀ is alkyl, aryl or amino depending on the group attached to the nitrile.

The preparation of cinnoline (X = N) and quinoline (X = CH) intermediates is outlined in Scheme 7.

20 Scheme 7

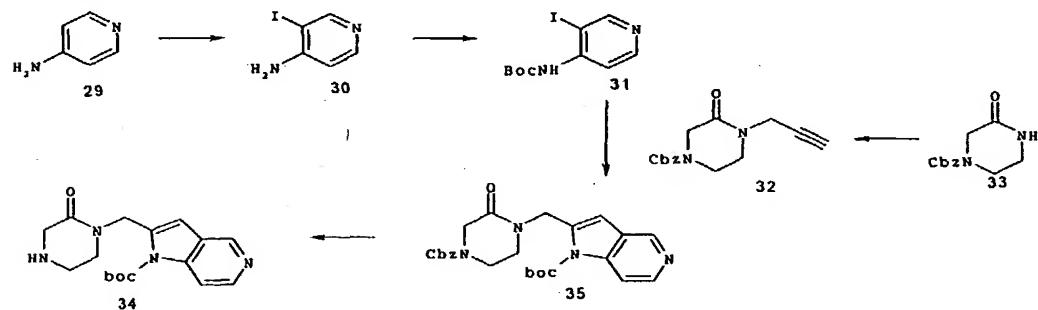


As shown in Scheme 7, halogenated azaarenes 23, exemplified by 4-chloro-7-trifluoromethylquinoline or cinnoline, are treated with H_2SO_4 (70 - 95 %) at 180-220 °C for about 16 to 48 hours in a sealed reaction vessel. The solution is cooled, poured into water and

5 neutralized with base to pH ~ 3-4. The product is dissolved in aqueous base and precipitated by acidification to yield 7-carboxy-4-chloroquinoline or cinnoline. This material is converted to the alkyl ester, such as methyl (24) or ethyl, by standard methods. 7-Alkyloxycarbonyl-4-chloroquinoline or cinnoline is dissolved in an anhydrous, aprotic solvent (THF or ether). The solution is cooled (-60 to -95 °C) and treated with a reducing agent such as lithium aluminum 10 hydride. The solution is warmed (to approximately -40 to -50 °C) for about 15 to 30 minutes and quenched with a solvent such as ethyl acetate. Standard workup gives the product 7-hydroxymethyl-4-chloroquinoline, or cinnoline (25). Material 25 is treated with 45-50 % HBr and heated to about 100-140 °C for about 45 to 90 minutes. After cooling and standard workup, 7-bromomethyl-4-chloroquinoline (or cinnoline) 26 is obtained. Alkylation as described before 15 provides 4-chloroquinoline (or cinnoline) 27 followed by deprotection under the usual acidic conditions gives 4-chloroquinoline (or cinnoline) 28.

The preparation of pyrrolopyridine derivatives is outlined in Scheme 8.

Scheme 8



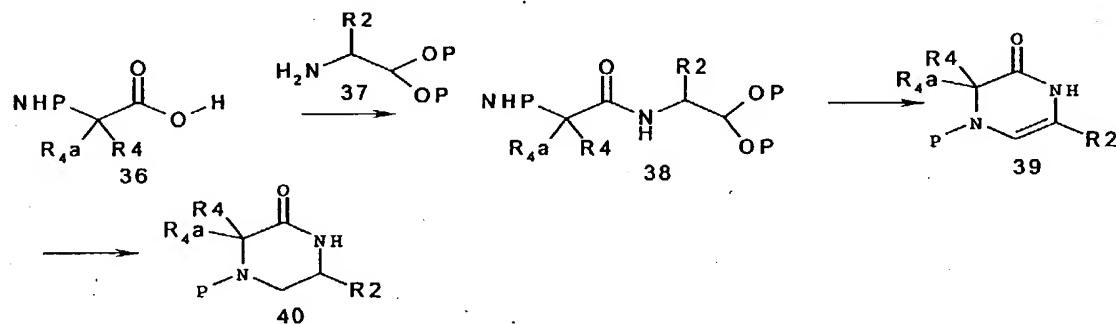
As indicated in Scheme 8, pyrrolopyridine derivatives are prepared by alkylation of a suitably protected oxopiperazine 33 with propargyl bromide in the presence of a base such as sodium hydride. The resulting alkyne 32 is heated (100-120 °C) with a halopyridine 31,

optionally substituted with hydroxy, alkoxy carbonylamino, or sulphydryl, a catalyst, such as $Pd(PPh_3)_2Cl_2$, copper iodide and triethylamine, in a suitable solvent, such as acetonitrile, in a sealed vessel or in DMF for 2-20 hours. When the pyridine is substituted with an alkoxy carbonylamino moiety, additional treatment with DBU at about 60 °C in DMF yields

5 pyrrolopyridine 35. Subsequent carbamate deprotection using transfer hydrogenation conditions such as Pd black in formic acid yields the desired oxopiperazine pyrrolopyridines 34. After further reaction of 34 with the L_1 -Cy₁ group, an additional deprotection step such as Boc removal using, for example, TFA, HCl is required for generating the oxopiperazine pyrrolopyridines with L_1 -Cy₁ in place. Halopyridine 31 is prepared from iodination of 4-10 aminopyridine 29 to give iodo-aminopyridine 30 followed by Boc protection.

The preparation of compounds of formula 40 is outlined in Scheme 9.

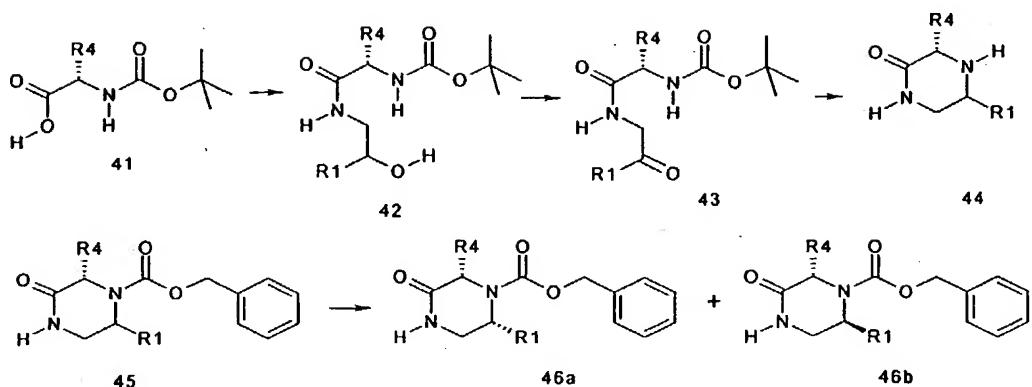
Scheme 9



15 As shown in Scheme 9, compounds of formula 40 are prepared from an appropriately protected mono- or di- substituted amino-acid 36. To this is added an amino-acetaldehyde, protected as an acetal derivative 37, under standard peptide coupling procedures, employing activating reagents such as EDC, TBTU, or BOP. The resulting dipeptidyl moiety 38 is subjected to conditions which remove the acetal, such as acidic conditions (TsOH). The 20 resulting cyclic material 39 is reduced using hydrogenating conditions to yield a compound of formula 40. This reduction, alternatively, can be carried out using a reagent which acts as a hydride source, such as LAH or NaH..

The preparation of compounds of formula 46a and 46b is outlined in scheme 10.

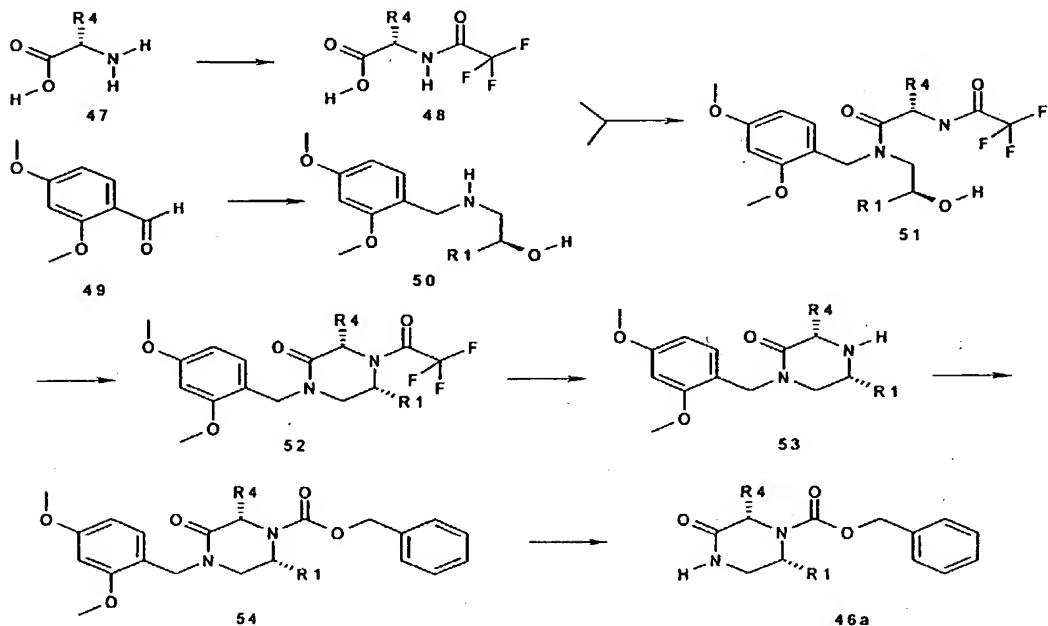
Scheme 10.



As indicated in Scheme 10, a protected amino acid 41 is coupled to a beta-aminoalcohol using standard peptide coupling procedures (iso-propyl chloroformate and triethylamine). The alcohol 42 is then oxidized to a ketone 43 using, for example, Swern oxidation conditions. The 5 protecting group is removed with trifluoroacetic acid and the resulting cyclized compound is reduced under hydrogenation conditions to give the 2-piperidinone 44. The piperazin-2-one ketopiperazine is reacted with N-(benzyloxycarbonyloxy)-succinimide to give a mixture of diastereomers 45 which are separated by chromatographic methods, or in some cases by recrystallization, to give compounds 46a and 46b.

10 A chiral synthesis of compounds of formula 46a is outlined in Scheme 11.

Scheme 11



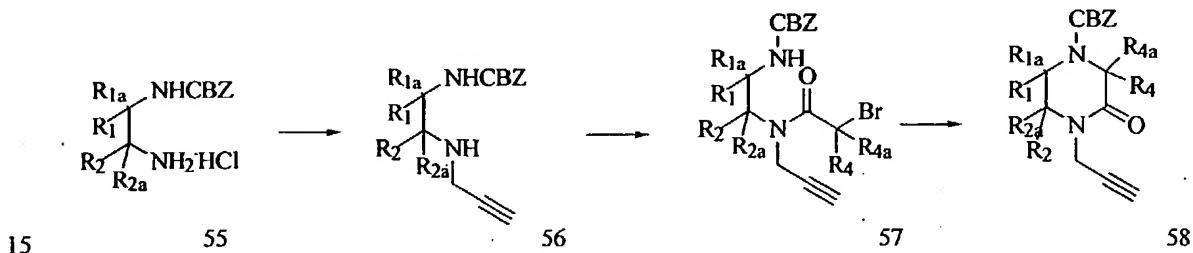
As shown in Scheme 11, amino acid 47 is protected as its trifluoroacetate derivative using trifluoroacetic anhydride and a base to yield compound 48. Amino-alcohol 50 is obtained via reductive amination conditions using a benzaldehyde derivative, such as 2,4-

dimethoxybenzaldehyde 49 and the corresponding primary amine. The resulting amino-alcohol 50 is then coupled to amino-acid 48 using standard peptide coupling procedures (iso-propyl chloroformate and triethylamine) to afford compound 51. Ring closure of compound 51 is then accomplished by utilizing Mitsinobu conditions to yield 2-piperidinone 52. The trifluoroacetate group of compound 52 is removed under basic conditions to give amine 53, which reacts with N-(benzyloxycarbonyloxy)succinimide to give carbamate 54. Deprotection of compound 54 is achieved with an aqueous solution of potassium persulfate and sodium phosphate and heat to produce compound 46a. All possible enantiomers of piperazin-2-one, shown in scheme 2c, can be made from the corresponding amino-alcohol 50 and amino acid 47.

10

The preparation of the compound of formula 58 wherein R₁, R₂, R_{2a}, R₄ and R_{4a} are hydrogen and R_{1a} is carbomethoxy, methoxymethyl, or a protected hydroxymethyl group is shown in Scheme 12.

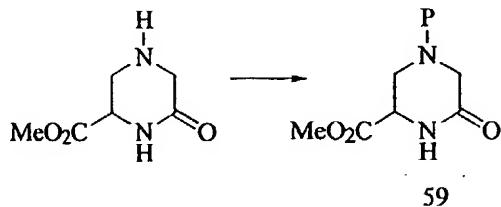
Scheme 12



As shown in Scheme 12, alkynylating a compound of formula 55 with propargyl bromide in the presence of an amine base such as triethylamine provides the compound of formula 56. Coupling with bromoacetic acid using a standard reagent such as DCC gives the compound of formula 57, which can be cyclized using a non-nucleophilic strong base, such as NaH, in a solvent, such as THF, to yield the desired compound of formula 58.

The preparation of a compound of formula 59 is outlined in Scheme 13.

Scheme 13

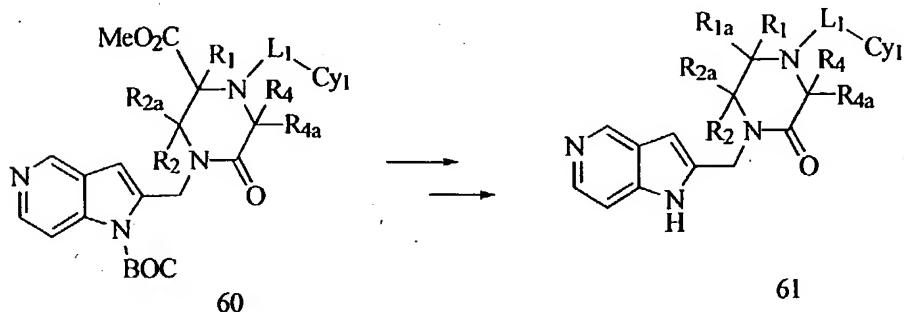


25 As indicated in Scheme 13, protection of methyl 6-oxopiperazine-2-carboxylate (Aebischer, B., *Helv. Chim. Acta* 1989, 72, 1043-1051) using, for example, benzyl chloroformate or allyl chloroformate under standard conditions provides compound 59.

Alkynylation of 59 with propargyl bromide using a strong base such as NaH in polar solvents as THF or DMF provides the compound of formula 58 (Scheme 12).

The preparation of a compound of formula 61 wherein R₁, R₂, R₄, R_{4a}, L₁ and Cy₁ are as defined in formula I above, and R_{1a} and R_{2a} are independently carboxy, acetamido or hydroxymethyl, is outlined in Scheme 14.

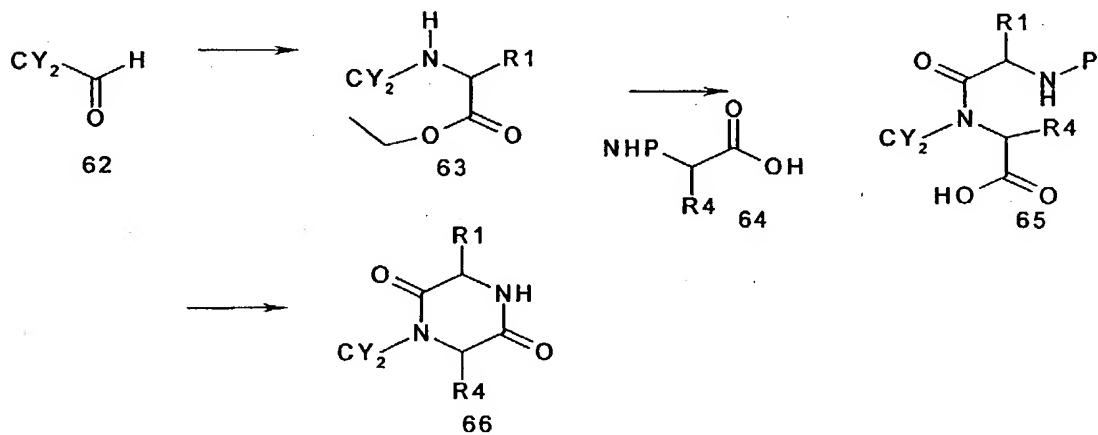
5 Scheme 14



As shown in Scheme 14, the compound of formula 61 is prepared by hydrolysis of the corresponding ester 60 using a base such as NaOH or LiOH to yield the acid 61. Coupling the acid with a primary or secondary amine or ammonia using standard coupling reagents such as TBTU or EDC gives the amide 61. Alternatively, reduction of the ester 60 using a reducing agent such as NaBH₄ yields a hydroxymethyl resin of 61.

The preparation of diketopiperazine compounds of formula 66 is outlined in Scheme 15.

15 Scheme 15

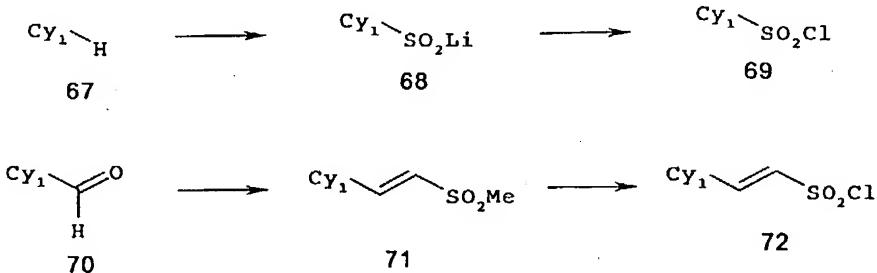


As shown in Scheme 15, an aldehyde 62 containing the Cy₂ group is condensed with an amino acid ester under reductive amination conditions. The resulting secondary amine 63 is then coupled to an N-protected amino acid 64. The resulting dipeptide 65 is deprotected which, 20 in general, results in cyclization to the N-Cy₂ diketopiperazine 66. Alternatively, for dipeptides

65 which do not cyclize, diketopiperazine 66 formation can be achieved using a peptide coupling reagent such as EDC, TBTU, or BOP.

The preparation of sulfonyl chloride intermediates 69 and 72 is outlined in Scheme 16.

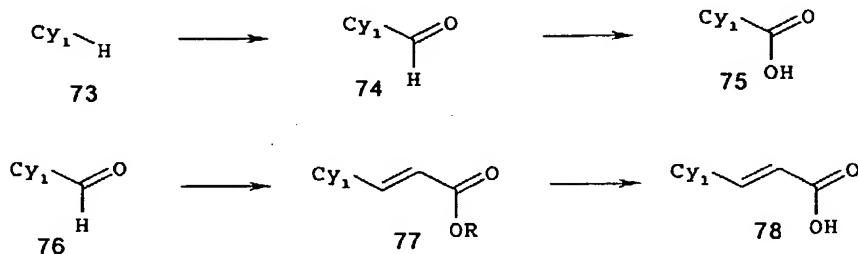
5 Scheme 16



As shown in Scheme 16, Cy₁ substituted sulfonyl chlorides 69 and 72 are prepared by treatment of the appropriate aryl or heteroaryl compounds 67 with a strong base such as n-BuLi at -78 °C followed by the addition of SO₂ gas and treatment of the resulting lithium aryl or heteroaryl sulfonate 68 with a chlorinating agent such as NCS or SO₂Cl₂ to yield compound 69 or, alternatively, by homologation of the appropriate aryl or heteroaryl aldehydes 70 using, for example, ethylmethanesulfonate to yield compound 71 and ethylchlorophosphonate to yield compound 72.

15 The preparation of intermediate compounds 75 and 78 of formula $Cy_1\text{-CO}_2\text{H}$ is outlined
in Scheme 17.

Scheme 17



As shown in Scheme 17, the requisite Cy₁ acids 75 and 78 can be obtained by oxidation of the corresponding alcohols or the aldehydes 74 using, for example, MnO₂, PDC or AgNO₃ in an appropriate solvent, such as CH₂Cl₂ or H₂O/EtOH. The Cy₁ substituted aryl and heteroaryl groups 73 can be functionalized by deprotonation methods using an appropriate non-nucleophilic base such as n-BuLi in an appropriate solvent such as Et₂O or THF and quenching with an appropriate carbonyl electrophile such as DMF, CO₂ or alkyl chloroformate.

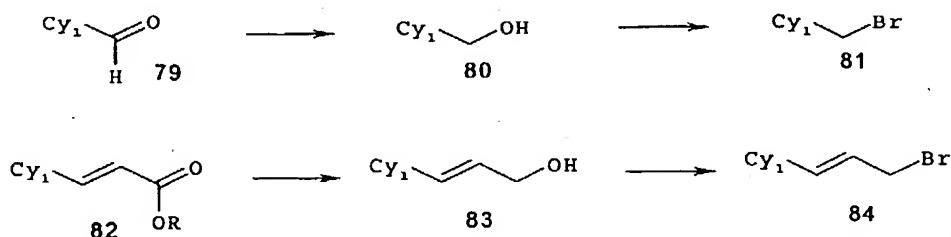
Alternatively, the acids can also be generated by hydrolysis of the corresponding esters 77

using, for example, NaOH or LiOH. For example, in the acrylic esters, the Cy₁-(alkenylene)- groups as defined above are generated by homologation of the Cy₁ aldehydes 76 using the usual Wittig type or Horner-Emmons type reagents in an appropriate solvent such as CH₂Cl₂ or THF.

5

The preparation of Cy₁ alkyl (81) and alkenyl (84) halides is outlined in Scheme 18.

Scheme 18



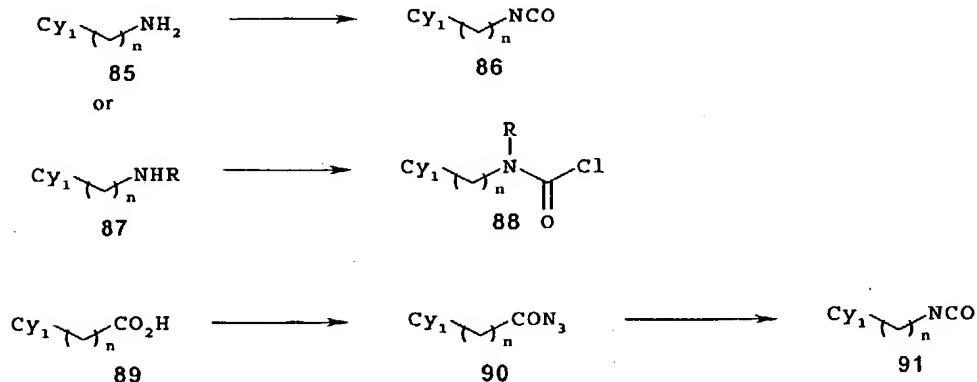
As shown in Scheme 18, Cy₁ alkyl and alkenyl halides 81 and 84 can be prepared by

10 halogenation of the corresponding alcohols 80 and 83 using either NBS, CBr₄ or PBr₃ under standard solvent conditions. The alcohols are generated by reduction of the corresponding aldehydes 79 or esters 82 using NaBH₄ or DIBAL in an appropriate solvent.

The preparation of Cy₁ isocyanate intermediates 86, 88 and 91 is outlined in Scheme

15 19.

Scheme 19



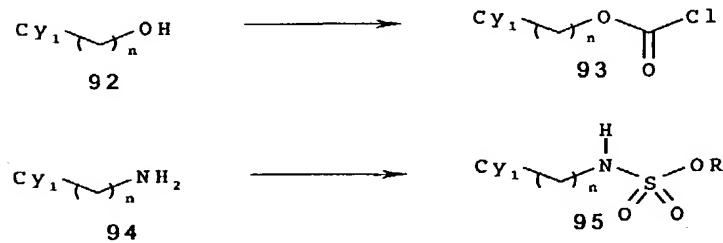
As shown in Scheme 19, Cy₁ isocyanates 86 and 88 are obtained by

chlorocarbonylation methods using phosgene or triphosgene in an appropriate solvent such as 20 CH₂Cl₂ with an appropriate base additive such as triethylamine or pyridine on the corresponding primary or secondary amines 85 and 87. Alternatively, the isocyanates 91 can also be generated by Curtius rearrangement in an appropriate solvent such as toluene, p-dioxane or DMF of the corresponding Cy₁ carbonyl azides 90. The carbonyl azides 90, in turn, are derived

from the corresponding carboxylic acids 89 using either DPPA reagent or by proceeding through the mixed anhydride via an alkyl chloroformate reagent in an appropriate solvent such as DMF or acetone and using an appropriate base additive such as triethylamine.

5 The preparation of Cy₁ chloroformate intermediates 93 and sulfamoyl esters 95 is outlined in Scheme 20.

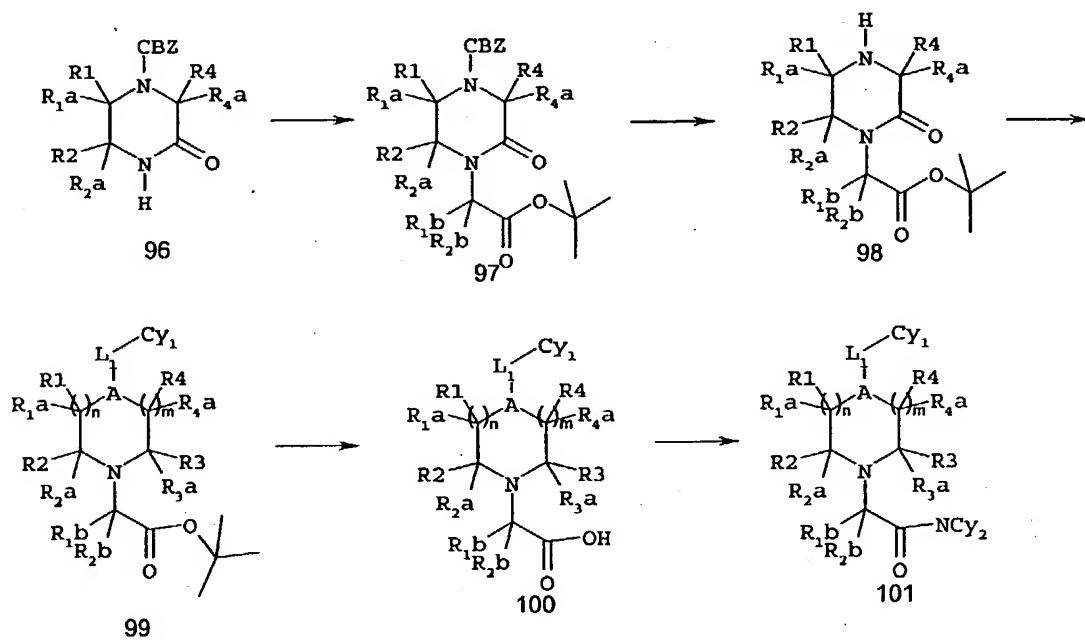
Scheme 20



10 As indicated in Scheme 20, Cy₁ chloroformates 93 are obtained by chlorocarbonylation of the corresponding alcohols 92 using reagents such as phosgene, triphosgene or 1,1'-carbonyldiimidazole in an appropriate solvent such as CH₂Cl₂. Activated sulfamyl esters 95 are prepared from the corresponding amines 94 using catechol sulfate in an appropriate solvent.

15 The preparation of acetamido compounds 101 of this invention is outlined in Scheme 21.

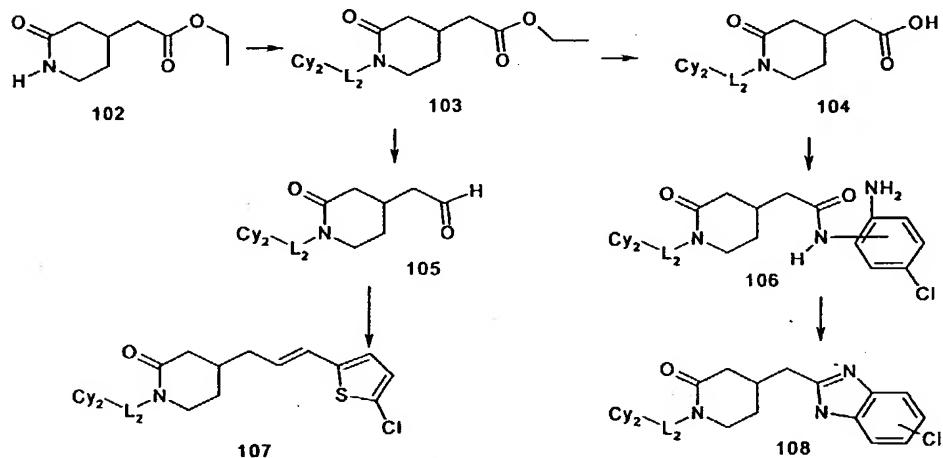
Scheme 21



As indicated in Scheme 21, alkylation of piperazin-2-one 96 is achieved with a strong base such as NaH and a t-butyl ester of haloacetic acid to give the acetate 97. Pd-catalyzed hydrogenation effects removal of the CBZ group from the acetate 97 to give amine 98, which is converted to the L₁-Cy₁ derivative 99 as described in Scheme 1 above. Hydrolysis of t-butyl ester 99 to the corresponding acid 100 is accomplished using, for example, TFA/CH₂Cl₂. The resulting acid 100 is coupled with the optionally protected amine HNCy₂ under typical amide bond formation conditions to give acetamide 101.

The preparation of compounds 107 and 108 of this invention wherein Cy₁ is benzimidazol-2-yl is outlined in Scheme 22.

Scheme 22

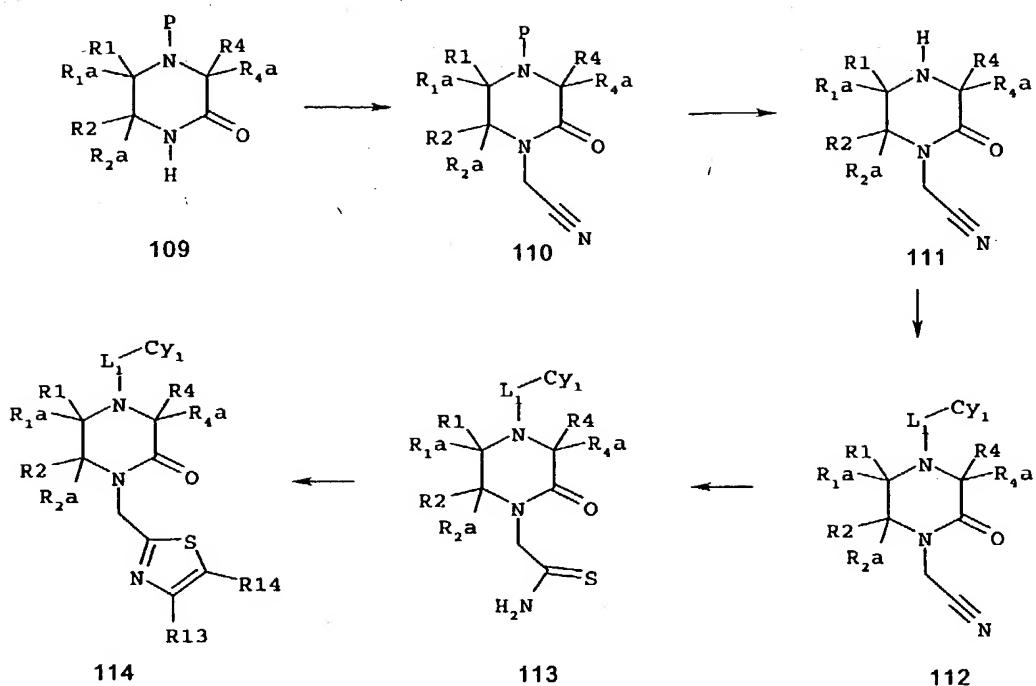


Piperidin-2-one 102 is alkylated by a procedure analogous to that described in Scheme 3 to give the N-Cy₂-L₂ ester derivative 103, which is hydrolyzed to give the acid 104 or reduced to 15 give aldehyde 105. Coupling of the acid 104 with an amine affords amide 106, which is cyclized with acetic anhydride to give the compound 108. Wittig-coupling of aldehyde 105 produces compound 107.

The preparation of the compound of formula 114 is outlined in Scheme 23, wherein R₁, R_{1a}, R₂, R_{2a}, R₄, R_{4a}, L₁, Cy₁, P, are defined in formula I and R₁₃ and R₁₄ are defined herein.

Scheme 23

61



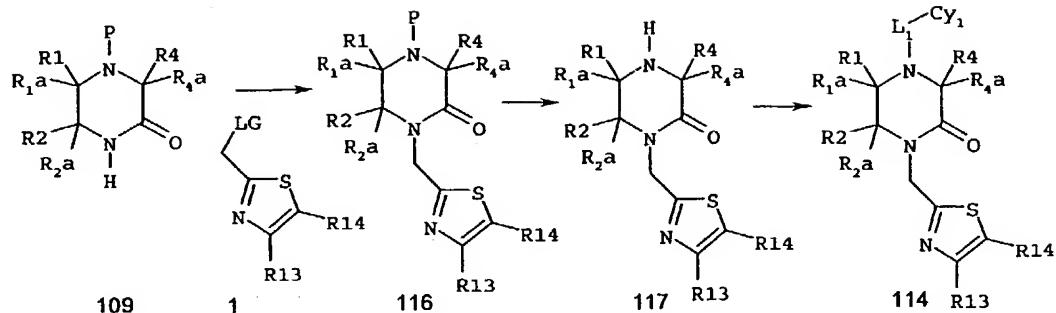
As shown in Scheme 23, alkylation of a compound of formula 109 with an appropriate

LG-CH₂-CN group wherein LG is a leaving group such as chloro, bromo, iodo, or optionally substituted lower alkylsulfonyloxy or arylsulfonyloxy in an inert organic solvent such as THF,

5 Et₂O or DMF in the presence of a strong base such as NaH, lithium hexamethyldisilylazide or lithium diisopropylamine provides a compound of formula 110. In a preferred aspect, P a tertiaryalkyl or aralkyl carbamate moiety. Removal of the group P can be accomplished by either strong acid such as TFA, a lewis acid or a reagent such as trimethylsilyl iodide to provide a compound of formula 111. Coupling of a compound of formula 111 with an appropriate LG-
 10 L₁-Cy₁ can be performed as previously described in Scheme 1 to give a compound of formula 112 in which the L₁-Cy₁ portion is a sulfonamide, alkyl amine, amide, urea, carbamate or sulfamyl urea. Reaction of a compound of formula 112 with hydrogen sulfide dissolved in ethanol, methanol or another suitable solvent, in the presence of diisopropylethylamine, triethylamine or another suitable base at an elevated temperature, preferably >80 °C, provides
 15 a compound of formula 113. A compound of formula 114 can be prepared by heating ketone groups of the formula, R₁₃-C(O)-CH(LG)-R₁₄, with a compound of formula 113 in a suitable high boiling solvent. LG is a leaving group as previously defined. If R₁₃ or R₁₄ contains a protecting group, this group can be removed at this point.

20 An alternative preparation of a compound of formula 114 (Scheme 23) is shown in Scheme 24.

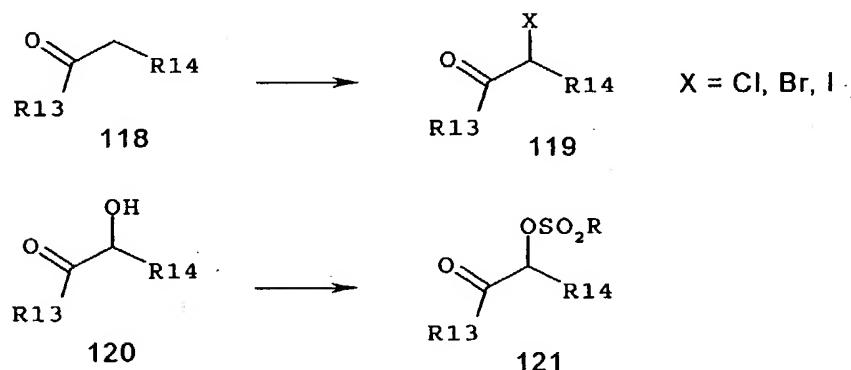
Scheme 24



A compound of formula 116 can be prepared from a compound of formula 109 using conditions previously described in Scheme 3 for the alkylation of $\text{Cy}_2\text{Lg}_2\text{-LG}$, which is represented by a compound of formula 115. Removal of the group P using a strong acid, strong base or reducing conditions provides a compound of formula 117. A compound of formula 114 is prepared from compound 117 using conditions previously described in Scheme 1.

10 The preparations of ketone groups of the formula, $R_{13}-C(O)-CH(LG)-R_{14}$ which are shown as compounds of formulas 119 and 121 are outlined in Scheme 25.

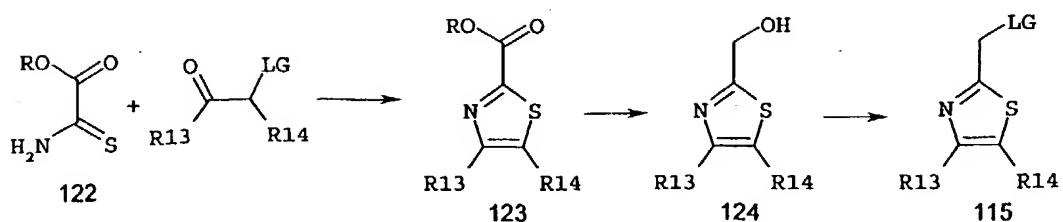
Scheme 25



15 Halogenation of a compound of formula 118 with an appropriate reagent such as thionyl chloride, bromine, bromine/HOAc, NBS or iodine produces the corresponding halide of formula 119. A compound of formula 120 can be reacted with a sulfonyl chloride and a suitable base such as pyridine or triethylamine to provide a compound of formula 121.

20 Preparation of thiazole of formula 115 is outlined in Scheme 26.

Scheme 26



Condensation of a thioamide compound of formula 122 with a ketone of the formula,

$R_{13}-C(O)-CH(LG)-R_{14}$ at elevated temperatures provides the thiazole compound of formula 123.

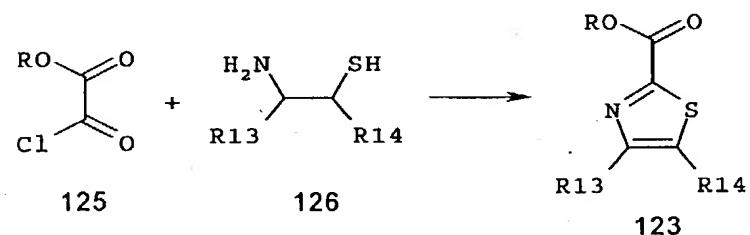
Reduction with LAH, DIBAL or a similar reagent provides the alcohol of formula 124.

5 Preparation of the compound of formula 115 can be achieved with PBr_3 to give the bromide (or with a sulfonyl chloride and base to provide the sulfonate ester).

An alternative preparation of a thiazole intermediate of formula 123 is outlined in

Scheme 27

10 Scheme 27



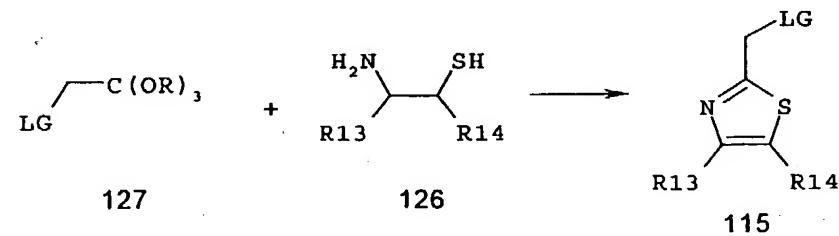
Condensation of a compound of formula 125 with an amino-thiol compound of formula 126 with a base such as pyridine provides a thiazole of formula 123. This method is especially useful in cases where R_{13} and R_{14} are combined to form an aromatic ring system.

15

An alternative preparation of a thiazole intermediate of formula 115 is outlined in

Scheme 28.

Scheme 28



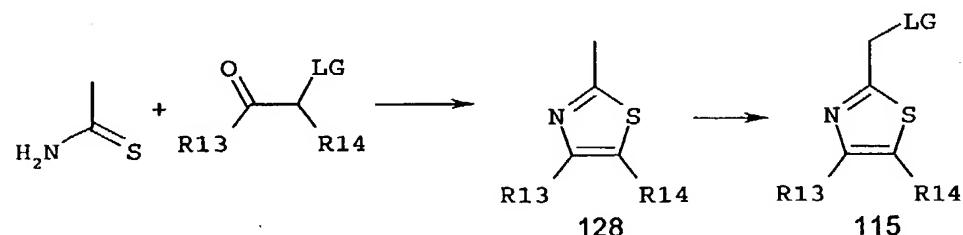
20 A compound of formula 127, such as 2-chloro-1,1,1-triethoxyethane, can be condensed with a compound of formula 126 at elevated temperatures to provide a compound of formula

115. This method is especially useful in cases where R_{13} and R_{14} are combined to form an aromatic ring system.

An alternative preparation of thiazole intermediate of formula 115 is outlined in Scheme

5 29.

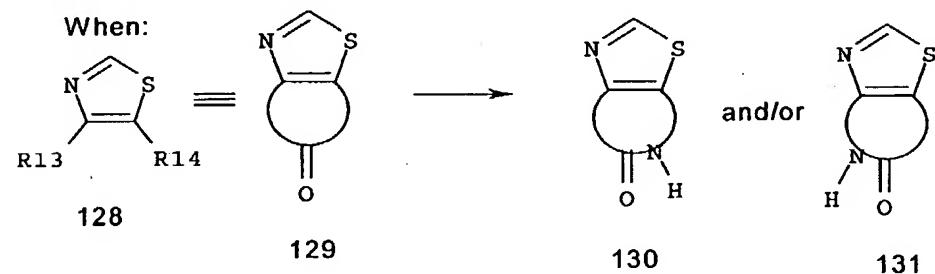
Scheme 29



Condensation of thioacetamide with a ketone of the formula, $R_{13}\text{-C(O)-CH(LG)-R}_{14}$ at an elevated temperature provides a thiazole of formula 128. Functionalization to provide a leaving group such as Br can be accomplished using NBS and an initiator at an elevated temperature in a solvent such as carbontetrachloride to provide a compound of formula 115. This method is especially useful in cases where R_{13} and R_{14} are combined to form an aromatic ring system.

15 Ring expansion of a compound of formula 128 to provide lactam products of formulas 130 and 131 is shown in Scheme 30.

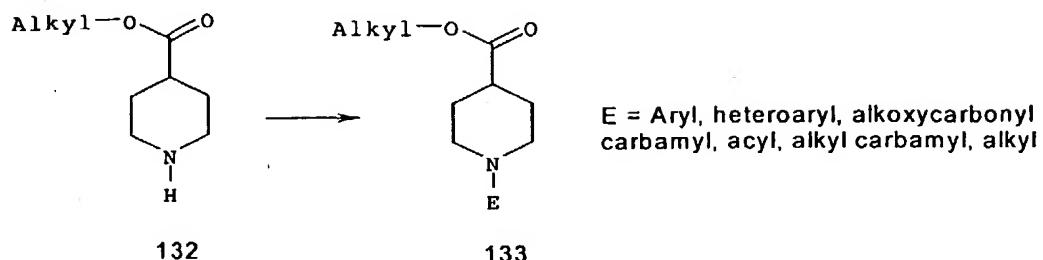
Scheme 30



When R_{13} and R_{14} are combined to form a carbocyclic ring containing a ketone as shown 20 in formula 21, then ring expansion to form the lactone products 130 and 131 can be achieved using the Schmidt reaction. At 0 °C to room temperature a mixture of the ketone 129 is stirred with sodium azide in sulfuric acid and chloroform. The Beckman ring expansion can also be used when the ketone 129 is first treated with hydroxylamine hydrochloride to give the intermediate oxime. An aniline byproduct can also be observed when the Semmler-Wolf aromatization mechanism predominates when thiazole-cycohexanone substrates are used.

Preparation of an intermediate of formula 133 is shown in scheme 31.

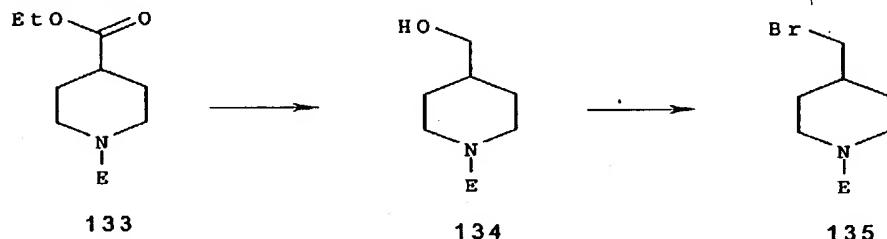
Scheme 31



5 When E of formula 133 aryl or heteroaryl, a compound of formula 133 can be prepared using a Pd catalyzed aromatic carbon-nitrogen bond forming reaction developed by Buchwald and Hartwig. This reaction has been reviewed (Acc. Chem. Res. 1998 31, 805-818) and can be generalized to include the reaction of an aromatic bromide, chloride or triflate in an inert solvent in the presence of a Pd (0) catalyst and a base such as sodium tert-butoxide, at an elevated 10 temperature, with a primary or secondary amine. When E of formula 133 is alkoxy carbonyl, acyl, alkyl carbamyl or alkyl, the corresponding halide can be used to couple to a compound of formula 132 in the presence of a base. When E of formula 133 is carbamyl, an isocyanate can be used to produce compound 133 from 132.

15 The preparation of a compound of formula 135 which can be used as an intermediate is outlined in Scheme 32.

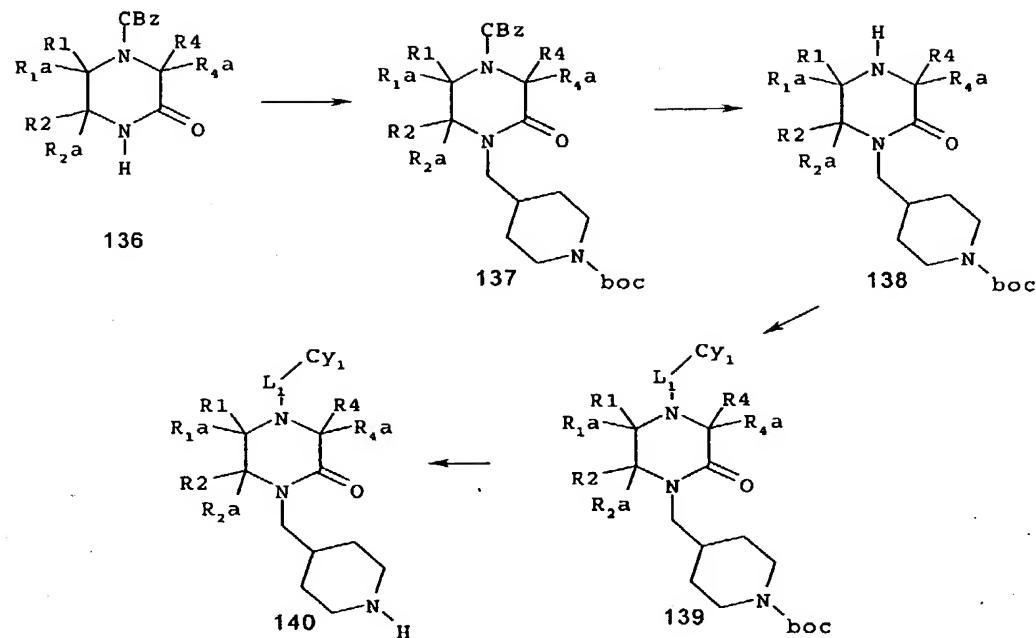
Scheme 32



Reduction of a compound of formula 133 with a reducing agent such as LAH, DIBAL or another similar reagent in a nonprotic solvent can provide an alcohol of formula 134. Conversion of the alcohol 134 into a good leaving group, such as the bromide, can be achieved using $\text{CBr}_4/\text{PPh}_3$ or another similar reagent to provide a compound of formula 135.

The preparation of the compound of formula 140, wherein R_1 , R_{1a} , R_2 , R_{2a} , R_4 , R_{4a} , L_1 ,
25 Cy_1 , are defined above is outlined in Scheme 33.

Scheme 33



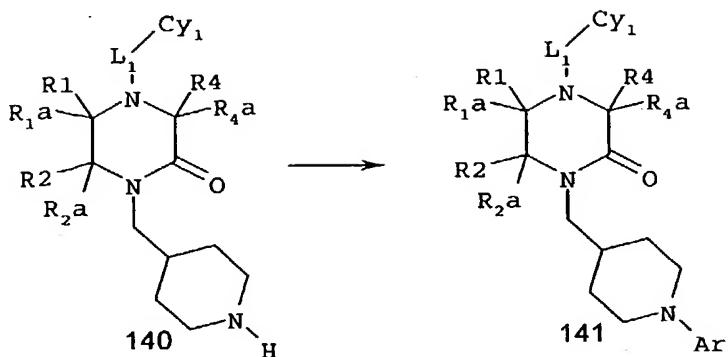
Alkylation of a compound of formula 136 with a compound of formula 135, where E is

5 tert-butoxycarbonyl, in an inert organic solvent such as DMF in the presence of a strong base
 such as NaH, lithium hexamethyldisilylazide or lithium diisopropylamine, provides a compound
 of formula 137. Removal of the CBz (benzyloxycarbonyl) group by catalytic hydrogenation in
 an appropriate solvent such as ethanol provides a compound of formula 138. Coupling of a
 compound of formula 138 with LG-L₁-Cy₁ can be performed as previously described above to
 10 give a compound of formula 139 in which the L₁-Cy₁ portion is a sulfonamide, alkyl amine,
 amide, urea, carbamate or sulfamyl urea. Removal of the Boc (t-butoxycarbonyl) group with a
 strong acid, such as TFA, provides a compound of formula 140.

Preparation of a compound of formula 141, where Ar is an aromatic ring, is shown in

15 scheme 34.

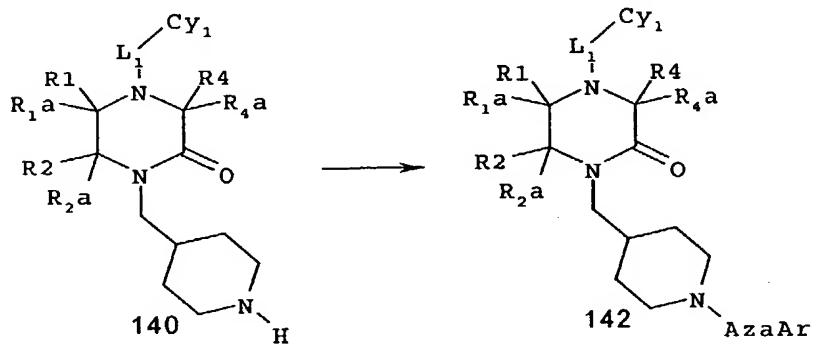
Scheme 34



A compound of formula 140 can be converted to a compound of formula 141 using a Pd catalyzed aromatic carbon-nitrogen bond forming reaction developed by Buchwald and Hartwig. This reaction has been reviewed (Acc. Chem. Res. 1998 31, 805-818) and can be generalized 5 to include the reaction of an aromatic bromide, chloride or triflate in an inert solvent in the presence of a Pd (0) catalyst and a base such as sodium tert-butoxide at an elevated temperature with a primary or secondary amine.

Preparation of a compound of formula 142, where AzaAr is an azaaromatic ring, is shown in 10 scheme 35.

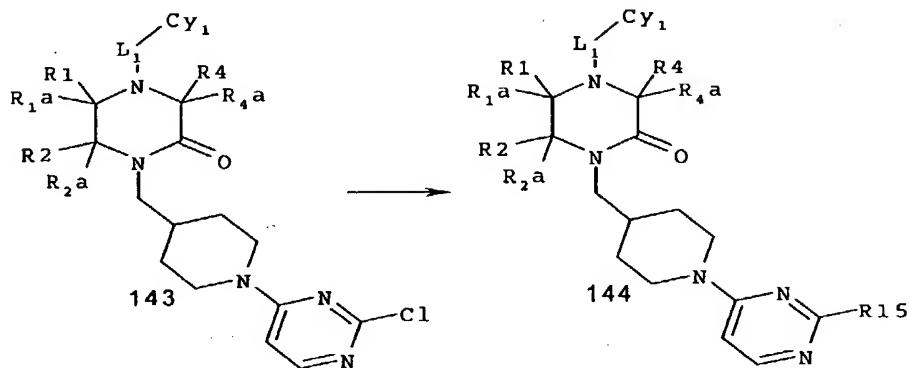
Scheme 35



A compound of formula 142 can be prepared from a halo-substituted azaheteroaromatic compound by heating the halo substituted compound with a compound of formula 140 at an elevated temperature in an inert high boiling solvent such as n-butanol, xylene or NMP. The types of azaheteroaromatic compounds which are best suited for this reaction employ a 15 halogen leaving group in a position of the ring which is activated toward displacement. Such systems are represented by, but not limited to, 2-fluoropyridine, 2-chloroquinoline, 2-chloropyrimidine, 4-chloro-pyrimidine and 2,4-dichloro-pyrimidine.

Preparation of a compound of formula 144, where R₁₅ is alkylamine, alkylether or alkylthio, is shown in scheme 36.

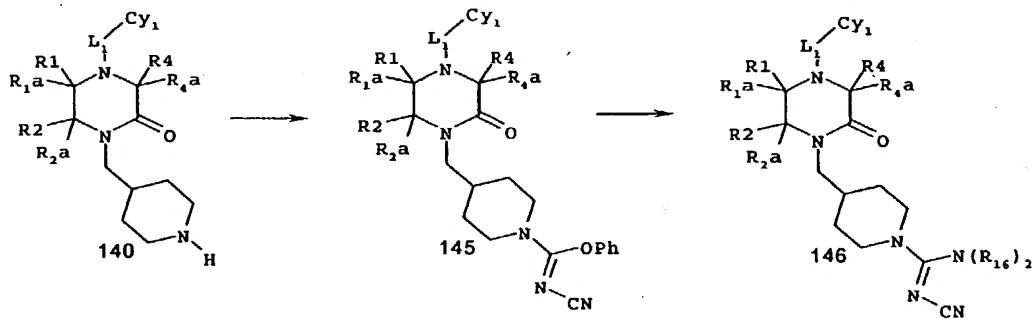
Scheme 36



5 A compound of formula 143 can be heated with either an amine, alcohol or thiol in an inert solvent to give the corresponding compound of formula 144.

Preparation of a compound of formula 145 and conversion to a compound of formula 146, where each R₁₆ is independently H or alkyl, is outlined in scheme 37.

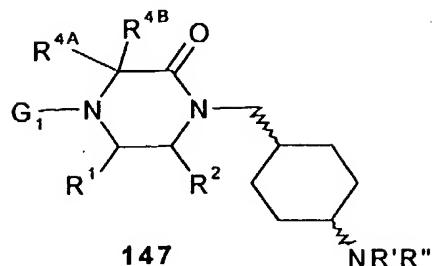
10 Scheme 37



15 A compound of formula 145 can be prepared by combining a compound of formula 140 with a reagent such as diphenyl cyanocarbonimidate at ambient temperature or with heating.

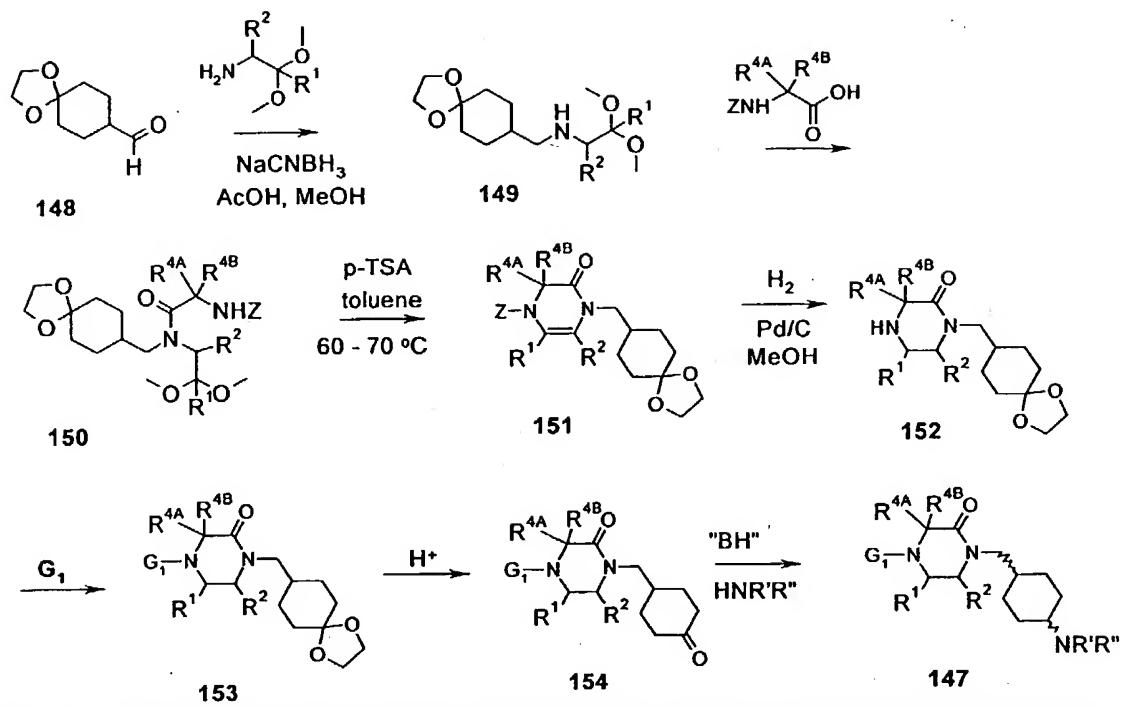
Heating compound 145 with amine NH(R₁₆)₂, where each R₁₆ is independently H or alkyl, in an inert solvent provides a compound of formula 146.

General Methods for the preparation of 1-(alkyl, aryl)amino-4-methylcyclohexylketopiperazines of Formula 147 are outlined in Scheme 38.

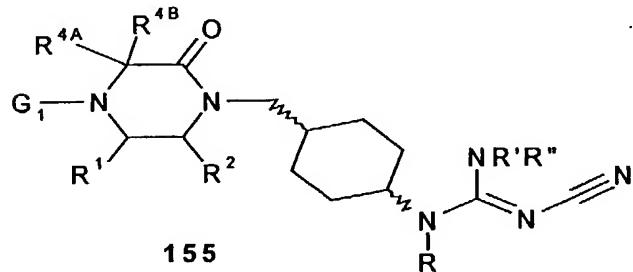


As indicated in the scheme 38, a preferred method of preparation of compounds of formula 147 involves construction of a ketopiperazine 152 containing the cyclic ketal of 4-methylcyclohexan-1-one as an N-1 substituent. Construction of intermediate 152 begins with reductive amination of intermediate 148 (prepared according to the method of Pearson et al.; *J. Org. Chem.* 62, 1997, 5284) with the substituted acetal of aminoacetaldehyde to provide intermediate 149. Intermediate 149 is then acylated with a suitably N-protected substituted α - amino acid to provide intermediate 150. Treatment of intermediate 150 with p-toluenesulphonic acid provides the unsaturated ketopiperazine 151. Deprotective hydrogenation of intermediate 151 provides intermediate 152. Attachment of the moiety G, provides intermediate 153. The acetal of the 4-substituted cyclohexanone is hydrolyzed under acidic conditions to provide intermediate 154. Reductive amination with the appropriate amine afford compounds of Formula 147. Reductive amination of the cyclohexanone with the selected amines can be achieved using standard methods known to those skilled in the art using borohydrides such as sodium borohydride or lithium tri-sec-butylborohydride in an appropriate solvent such as methanol or acetic acid at temperatures between 0 and 100 °C. The isomeric cis/trans products of reductive amination can be separated by silica-gel chromatography or RP-HPLC.

Scheme 38



General Methods for the preparation of 1-(N,N'-aryl/alkyl-cyanoguanidine)-4-methylcyclohexylketopiperazines of Formula 155 are outlined in scheme 39.

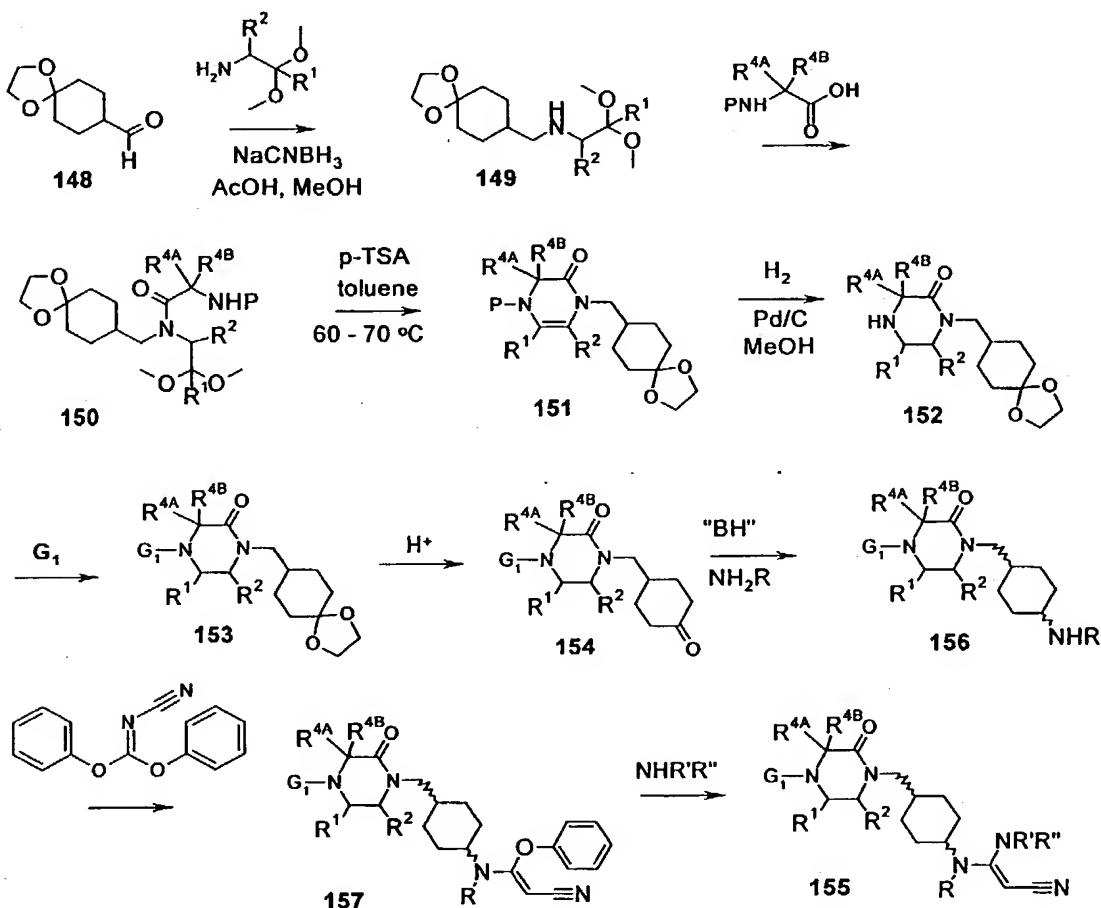


- 5 As shown in scheme 39, a preferred method of preparation of compounds of formula 155 involves construction of a ketopiperazine 152 containing the cyclic ketal of 4-methylcyclohexan-1-one as an N-1 substituent. Construction of intermediate 152 begins with reductive amination of intermediate 148 (prepared according to the method of Pearson et al.; *J. Org. Chem.* 62, 1997, 5284) with the substituted acetal of aminoacetaldehyde to provide intermediate 149.
- 10 Intermediate 149 is then acylated with a suitably N-protected substituted α -amino acid to provide intermediate 150. Treatment of intermediate 150 with p-toluenesulphonic acid provides the unsaturated ketopiperazine 151. Deprotective hydrogenation of intermediate 151 provides intermediate 152. Attachment of the moiety G1 provides intermediate 153. The acetal of the 4-substituted cyclohexanone is hydrolyzed under acetic conditions to provide intermediate 154.
- 15 Reductive amination with the appropriate primary amine provides intermediate 156. Reductive amination of the cyclohexanone with the selected amines can be achieved using standard

methods known to those skilled in the art using borohydrides such as sodium borohydride or lithium tri-sec-butylborohydride in an appropriate solvent such as methanol or acetic acid at temperatures between 0 and 100 °C. The isomeric cis/trans products of reductive amination can be separated by silica-gel chromatography or RP-HPLC. Intermediate 156 is reacted with diphenyl cyano-carbonimidate to provide intermediate 157. Intermediate 157 is reacted with appropriate primary and secondary amines to provide a compound of Formula 155.

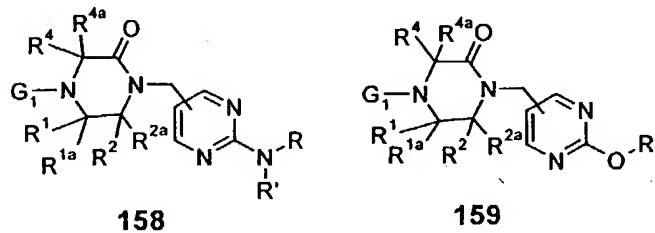
5

Scheme 39



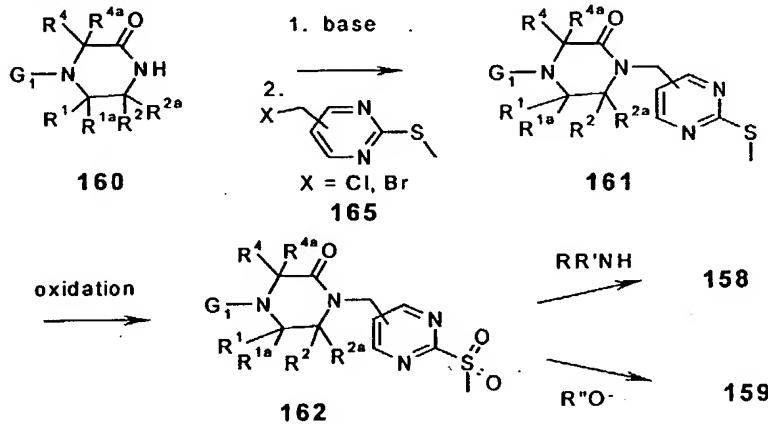
General Methods for the preparation of 2-substituted-4&5-methylpyrimidyl-

10 ketopiperazines of Formulas 158 & 159 are outlined in Scheme 40 below.



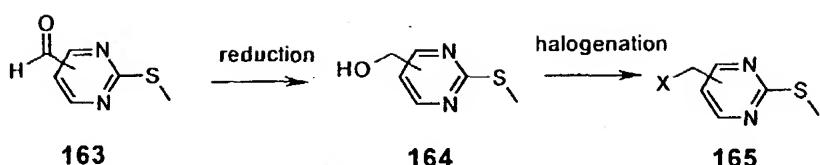
As shown in scheme 40, a preferred method of preparation of compounds of formula 158 and 159 involves alkylating a ketopiperazine intermediate 160 containing a desired N-4 substituent (designated G-1) with either 4 or 5-halomethyl 2-thiomethylpyrimidine to provide intermediate 161. Oxidation of the thiomethyl group of intermediate 161, to provide intermediate 162, followed by displacement with the appropriate amine or alkoxide affords compounds of Formula 158 or 159, respectively. Alkylation of the amide of intermediate 160 can be achieved using standard methods known to those skilled in the art such as deprotonation with NaH in DMF or *t*-butoxide in *t*-butanol at temperatures between -78 and 100°C followed by addition of the halide intermediate 165 and stirring at 0 to 100°C for 0.5 hours to 24 hours. Oxidation of the sulfide of intermediate 161 to the sulfone of intermediate 162 can be accomplished in standard fashion, such as using oxone in a mixture of MeOH and H₂O or *m*-CPBA in CH₂Cl₂. Displacement of the sulfone of intermediate 162 with the appropriate amine can be achieved by simply stirring the components neat or in an unreactive solvent such as CH₂Cl₂ or DMF for 0.5 to 24 hours at 20 to 100°C. Similarly, reaction of an alkoxide in an inert solvent leads to the desired displacement product.

Scheme 40



The 4&5-halomethyl-2-methylthiopyrimidines intermediates 165 can be prepared as illustrated in scheme 41 from the corresponding 4&5-carboxaldehydes intermediate 163, respectively. 2-Methylthiopyrimidine-4-carboxaldehyde can be prepared using the procedure of Bredereck et al. (*Chem. Ber.* 1964, 3407). 2-Methylthiopyrimidine-5-carboxaldehyde can be prepared by the procedure of Gupton et al. (*J. Het. Chem.* 28, 1991, 1281).

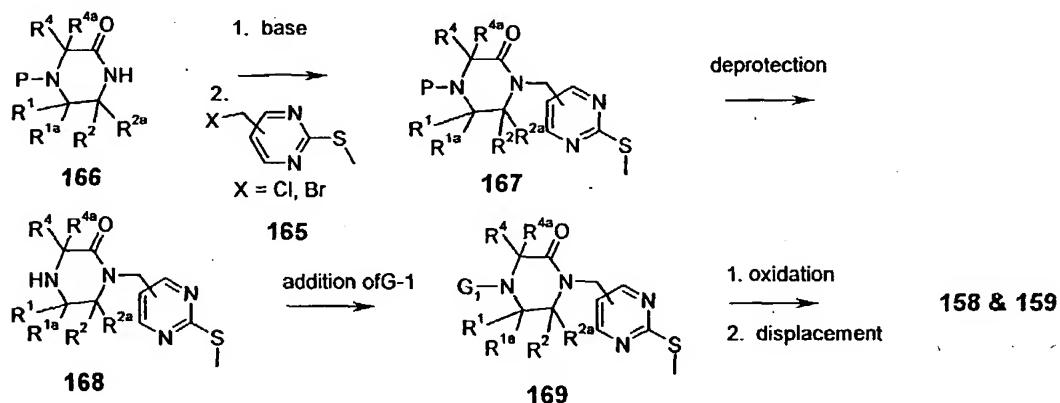
Scheme 41



Alternatively, as illustrated in scheme 42, compounds of formula 158 and 159 can be prepared by alkylating suitably protected [at N-4 (designated P)] ketopiperazine intermediate 166, with either the 4- or 5-halomethyl-2-methylthiopyrimidine (intermediate 165) to provide 5 intermediate 167. The protecting group of intermediate 167 can then be removed to provide intermediate 168 and the desired G-1 substituent added to provide intermediate 169. Suitable protecting groups include Boc, Cbz, Alloc and Fmoc, which can be manipulated in the usual manner.

Scheme 42

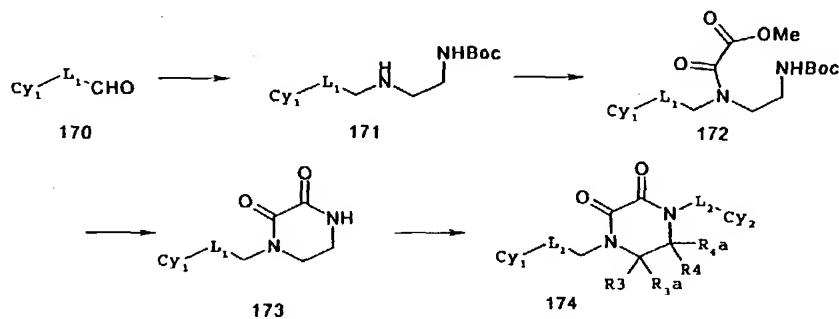
10



Diketopiperazine compounds of formula I, in which A is N, both R₁ and R_{1a} taken together and R₂ and R_{2a} taken together are oxygen, are prepared in general as described in *J. Org. Chem.* 1998, 63, 4131 and *Chem. Pharm. Bull.* 1981, 29, 684. The synthetic route used is outlined in Scheme 43 below.

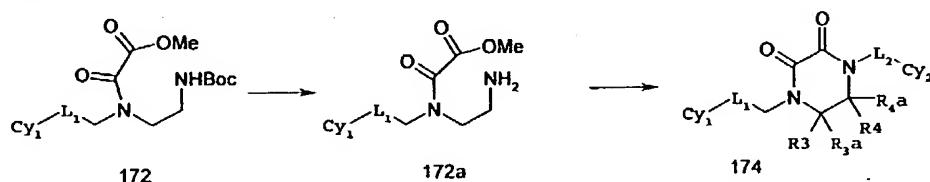
15. outlined in Scheme 43 below.

Scheme 43



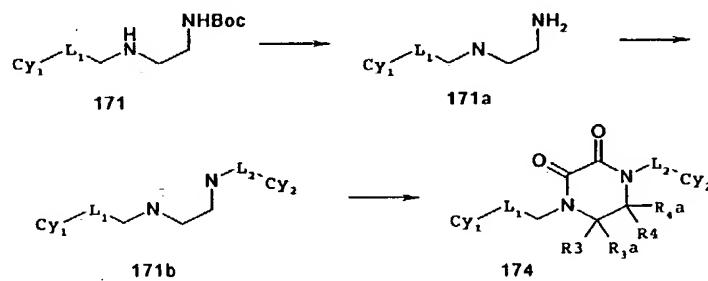
As shown in Scheme 43 above, an aryl, heteroaryl or biaryl aldehyde or alkenyl aldehyde derivatives representative of Cy₂-L₁ groups defined herein can be aminated with a suitably protected form of ethylenediamine using a reducing agent such as sodium borohydride. The secondary amine 171 is treated with an appropriate form of oxalyl chloride, notably methyl chlorooxacetate, in the presence of base to form oxalamic ester intermediate 172. 2,3-Diketopiperazine 203 is formed by removal of the protecting group under acidic conditions (HCl or TFA) followed by cyclization under base conditions (TEA). Appropriate Cy₂-L₂ groups can be appended to compounds of formula 173 by alkylation with a suitable aryl chloromethyl or bromomethyl ring system, such as a compound of formula 179 using NaH, LiN(SiMe₃)₃, NaN(SiMe₃)₃, LDA, or an appropriate base, in an inert solvent such as THF or DMF to provide compounds of formula 174 in which Cy₂ is a chloroquinazoline, chloroquinoline, aminoquinazoline or another group defined herein.

Scheme 43A



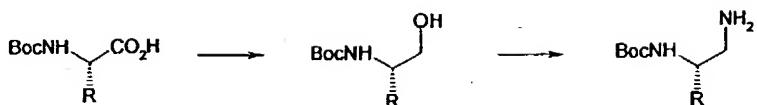
15 As shown in Scheme 43 A above deprotection of oxalamic ester intermediate 172 under acidic conditions can also be used to isolate intermediate 172a (Scheme 43A) and followed directly by reductive amination conditions with aryl aldehydes to incorporate the respective $Cy_2^-L_2$ groups using a reducing agent such as sodium borohydride or sodium cyanoborohydride. Ring closure occurs under these conditions to provide the 2,3-diketopiperazines 174 *in situ*.

Scheme 43B



Alternatively, the route shown above in Scheme 43B can be used by deprotecting the secondary amine 171 under acidic conditions (HCl or TFA) to diamine 171a and followed directly by reductive amination with aryl aldehydes to incorporate the respective Cy₂-L₂ groups using a reducing agent such as sodium borohydride or sodium cyanoborohydride. Diamine 171b is then cyclized by reacting with dimethyl oxalate to provide 2,3-diketopiperazines 174.

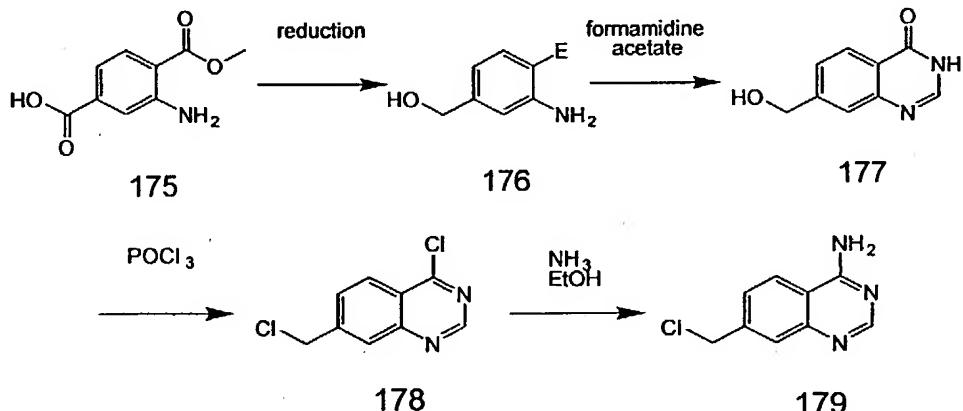
Scheme 43C



As shown in Scheme 43 C above substituted unsymmetrical ethylenediamine units can

5 be employed by preparing from corresponding amino acids (Scheme 43C). Formation of the mixed anhydride from the acid moiety (iso-butyl chloroformate) followed by reduction (sodium borohydride) gives the respective amino alcohol intermediate. The alcohol moiety can be derivatized as the mesylate (methanesulfonyl chloride), converted to the azide (sodium azide) and reduced by hydrogen to generate the appropriately protected ethylenediamines.

10 Scheme 44



As shown in Scheme 44, the quinazoline 179 can be prepared by reduction of the acid 175 with Super Hydride in THF to afford the alcohol 176. The alcohol 176 is then reacted in 15 formamide at about 180°C to afford cyclised compound 177. The cyclised compound 177 is then converted to its chloro derivative 178, by reacting with POCl_3 . The chloro derivative 178 is then converted to the amino compound 179 by using NH_3 in ethanol or $\text{NH}_4\text{OAc}/\text{PhOH}$.

This invention is further exemplified but not limited by the following examples which further illustrate the preparation of the compounds of this invention. The starting materials and 20 intermediates are prepared by the application or adaptation of known methods, for example methods used heretofore or described in the literature, for example those described by R. C. Larock in Comprehensive Organic Transformations, VCH publishers, 1989.

The compounds of the invention, their methods of preparation and their biological 25 activity will appear more clearly from the examination of the following examples which are presented as an illustration only and are not to be considered as limiting the invention in its scope.

EXAMPLE 1. 6-Chlorobenzo[b]thiophene-2-sulfonyl chloride.A. 1-Chloro-3-(2,2-dimethoxyethylsulfanyl)benzene.

To a solution of 3-chlorothiophenol (2.4 g, 16.6 mmol) in THF (200 mL) at 0°C is added 5 bromoacetaldehyde dimethyl acetal (2.8 g, 16.6 mmol). To the solution is added sodium hydride (60% mineral oil dispersion, 0.70 g, 17.4 mmol). The reaction is stirred for 16 hours, and then is quenched by the addition of saturated NH₄Cl (aq.). The solution is diluted with EtOAc. The organic layer is washed with a saturated NaCl (aq.). The organic layer is dried over MgSO₄, filtered and concentrated. The crude product is purified by column 10 chromatography eluting with hexanes. The title compound (3.7 g, 15.9 mmol) is obtained as an oil. ¹H NMR (CDCl₃, 300MHz) δ 7.32 (m, 1H), 7.25 (m, 1H), 7.12 (m, 1H), 4.47 (m, 1H), 3.07 (s, 3H), 3.02 (s, 3H).

B. 4-Chlorobenzo[b]thiophene and 6-Chlorobenzo[b]thiophene.

A solution containing polyphosphoric acid (8 g) and chlorobenzene (50 mL) is heated at 15 reflux. A solution containing 1-chloro-3-(2,2-dimethoxyethylsulfanyl)benzene (2.7 g, 11.6 mmol) in chlorobenzene (5 mL) is added dropwise to the refluxing polyphosphoric acid solution. After 6 hours, the solution is cooled to ambient temperature. The solution is diluted with CH₂Cl₂ and washed with water and saturated NaCl (aq.). The organic layer is dried over MgSO₄, filtered and concentrated. The crude product is purified by column chromatography eluting with 20 hexanes to yield the title compounds (2.4 g, 9.0 mmol) as a 1:1 isomeric mixture. ¹H NMR (CDCl₃, 300MHz) δ 7.88 (m, 1H), 7.75 (m, 2H), 7.42 (m, 2H). MS (EI): m/z 168, 170 (M+), Cl pattern.

C. 4-Chlorobenzo[b]thiophene-2-sulfonyl chloride and 6-Chlorobenzo[b]thiophene-2-sulfonyl chloride.

25 To a solution of 4-chloro-benzo[b]thiophene and 6-chlorobenzo[b]thiophene (11.8 g, 88.1 mmol), in 400 mL of THF at -78°C is added n-BuLi (55 mL of a 1.6M solution in hexanes, 88.1 mmol). After 15 minutes, the solution is added by cannula to a precooled (-78°C) solution of SO₂ (200 g) in 100 mL of THF. After addition, the solution is allowed to warm to ambient temperature. After 0.5 hour, the solution is concentrated. The residue is suspended in 30 hexanes (400 mL) and is cooled to 0°C. To the solution is added SO₂Cl₂ (12.5 g, 92.5 mmol). After stirring for 15 minutes, the solution is concentrated. The residue is dissolved in EtOAc. The organic solution is washed with saturated NH₄Cl (aq.), H₂O and saturated NaCl (aq.). The organic layer is dried over MgSO₄, filtered and concentrated. The crude product is dissolved in CH₂Cl₂ and filtered through a plug of silica gel. The crude product is purified by column

chromatography eluting with hexanes to yield the title compound as well as 4-chlorobenzo[b]thiophene-2-sulfonyl chloride as white solids.

4-Chlorobenzo[b]thiophene-2-sulfonyl chloride: ^1H NMR (CDCl₃, 300MHz) δ 8.32 (m, 1H), 7.81 (m, 1H), 7.53 (m, 2H).

5 6-Chlorobenzo[b]thiophene-2-sulfonyl chloride: ^1H NMR (CDCl₃, 300MHz) δ 8.11 (s, 1H), 7.88 (m, 2H), 7.50 (m, 1H).

EXAMPLE 2. 5'-Chloro-[2,2']bithiophenyl-5-sulfonyl chloride.

A. 5-Chloro-[2,2']bithiophene.

10 The title compound is prepared from 2-chloro-thiophene according to the procedure described in Bull. Chem. Soc. Japan, 1979, 1126. The crude product is purified by column chromatography eluting with a gradient of 5% EtOAc/hexanes to 10% EtOAc/hexanes to afford a white solid. ^1H NMR (CDCl₃, 300MHz) δ 7.24 (m, 1H), 7.11 (d, 1H), 7.03 (dd, 1H), 6.94 (d, 1H), 6.83 (d, 1H). MS (EI) [M+] = 200, 202, Cl pattern.

15 B. 5'-Chloro-[2,2']bithiophenyl-5-sulfonyl chloride.

The title compound is prepared as described in Example 1, Part C using 5-chloro-[2,2']bithiophene in place of 6-chloro-benzo[b]thiophene. The crude product is purified by column chromatography eluting with a gradient of 5% EtOAc/hexanes to 10% EtOAc/hexanes to give a white solid. ^1H NMR (CDCl₃, 300MHz) δ 7.76 (d, 1H), 7.14 (d, 1H), 7.09 (d, 1H), 6.92 (d, 1H). MS (EI): m/z 298, 300 (M+), Cl pattern.

EXAMPLE 3. 2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl chloride.

A. 2-(5-Chloro-thiophen-2-yl)-ethenesulfonic acid ethyl ester.

n-Butyllithium (53.1 mL, 2.5M solution in hexanes) is added dropwise to a solution of ethylmethanesulfonate (12.9 mL, 0.12 mol) in THF (300 mL) at -78°C. The reaction mixture is stirred for 15 min then ethylchlorophosphonate (9.9 mL, 0.07 mol) is added dropwise. The solution is stirred at -78°C for 30 minutes and then heated to 50°C for 1 hour. The reaction mixture is then cooled to -78°C and stirred for 1 h then 5-chlorothiophenecarboxaldehyde (7.1 mL, 0.07 mol) is added dropwise. The reaction mixture is allowed to slowly warm to RT overnight. Water (30 mL) is added to the mixture and stirred for 15 min then concentrated in vacuo. The residue is taken up in CH₂Cl₂ and washed with water, brine, dried over MgSO₄, filtered and concentrated to dryness. The crude product is purified by column chromatography eluting with 5% EtOAc/hexanes to give title product (11.3 g, 0.04 mol) as an oil. ^1H NMR (CDCl₃, 300MHz) δ 7.51 (d, 1H), 7.10 (d, 1H), 6.91 (d, 1H), 6.42 (d, 1H), 4.20 (q, 2H), 1.40 (t, 3H).

B. 2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl chloride.

Tetrabutylammonium iodide (16.3 g, 44.2 mmol) is added to a solution of 2-(5-chloro-thiophen-2-yl)-ethenesulfonic acid ethyl ester (11.3 g, 40.2 mmol) in acetone (100 mL) at room temperature. The mixture is heated to reflux and stirred overnight then cooled to RT and 5 concentrated in vacuo. The residue is taken up in CH_2Cl_2 then washed with water and brine. The organic layer is dried over MgSO_4 , filtered and concentrated to dryness to give an oil (18.74 g, 40.2 mmol) which is taken on to the next step without further purification. Sulfuryl chloride (7.1 mL, 88.5 mmol) is added to a solution of triphenylphosphine (21.0 g, 86.42 mmol) in CH_2Cl_2 at 0°C. The ice bath is then removed and the product (18.74 g, 40.2 mmol) from the above 10 reaction is added. After 2 h, the reaction mixture is concentrated in vacuo and the product purified by column chromatography eluting with 10% EtOAc/Hexanes to give the title compound (6.4 g, 26.3 mmol) as an off-white solid. ^1H NMR (CDCl_3 , 300 MHz) δ 7.70 (d, 1H), 7.23 (d, 1H), 7.00 (d, 1H), 6.91 (d, 1H).

15 EXAMPLE 4. 3-Chlorobenzyl sulfamyl catechol.

To a solution of 3-chlorobenzylamine (0.14 g, 1.0 mmol) in 3 mL of DMF is added Et_3N (0.10 g, 1.5 mmol). The solution is cooled to 0°C. Catechol sulfate (0.172 g, 1.0 mmol) is added. The solution is warmed to ambient temperatures. After 2.5 h, 30 mL of EtOAc is added. The solution is washed with 5% HCl, H_2O and saturated NaCl. The organic layer is dried over 20 MgSO_4 , filtered and concentrated to give the title compound (0.30 g, 0.97 mmol). ^1H NMR (d_6 -DMSO, 300 MHz) δ 9.94 (s, 1H), 8.82 (m, 1H), 7.41 (m, 4H), 7.19 (d, 1H), 7.10 (m, 1H), 6.95 (d, 1H), 6.79 (m, 1H), 4.32 (AB, 2H).

EXAMPLE 5. 2-Bromomethyl-6-chlorobenzo[b]thiophene.25 A. 6-Chlorobenzo[b]thiophene-2-carboxaldehyde.

To a solution of 6-chlorobenzo[b]thiophene (1.0 g, 5.93 mmol) in THF (60 mL) at -78°C is added a 1.6 M solution of n-BuLi in THF (3.9 mL, 6.23 mmol). After 10 minutes, 0.5 mL of DMF is added. The solution is stirred for 0.5 hours, then allowed to warm to ambient 30 temperature. The solution is poured into a solution of saturated NH_4Cl . The solution is diluted with ether and the layers are separated. The organic layer is washed with H_2O and saturated NaCl. The organic layer is dried over MgSO_4 , filtered and concentrated. The title compound is obtained as a white solid. MS (EI): m/z 196 (M+).

B. 6-Chlorobenzo[b]thiophen-2-yl)methanol.

To a solution of 6-chlorobenzo[b]thiophene-2-carboxaldehyde in THF at 0°C is added 35 NaBH_4 . After 1 hour, the solution is diluted with saturated NH_4Cl and ether. The organic layer

is washed with H_2O and saturated $NaCl$, dried over $MgSO_4$, filtered and concentrated. 1H NMR ($CDCl_3$, 300 MHz) δ 7.82 (s, 1H), 7.60 (d, 1H), 7.40 (m, 2H), 4.91 (AB, 2H).

C. 2-Bromomethyl-6-chlorobenzo[b]thiophene.

To a solution of 6-chlorobenzo[b]thiophen-2-yl)-methanol (0.2 g, 1.01 mmol) in THF (10 mL) is added triphenyl phosphine (0.34 g, 1.31 mmol) followed by CBr_4 (0.42g, 1.26 mmol). After 3 hours, the solution is concentrated. The product is purified by column chromatography eluting in a gradient of 5% EtOAc/hexanes to 10% EtOAc/hexanes. The product is obtained as a white solid (0.25 g, 0.53 mmol). 1H NMR ($CDCl_3$, 300 MHz) δ 7.82 (s, 1H), 7.62 (d, 1H), 7.40 (m, 2H), 4.76 (s, 2H).

10

EXAMPLE 6. 5-Bromomethyl-5'-chloro-[2,2']bithiophenyl.

A. (5'-Chloro-[2,2']bithiophenyl-5-yl)-methanol.

To a solution of 5-chloro-[2,2']bithiophenyl (3.00 g, 14.9 mmol) in 30 mL of THF at 0°C is added n-BuLi (9.8 mL of a 1.6M solution in hexanes, 15.7 mmol) dropwise. DMF (2.30 mL, 30 mmol) is added dropwise and the resulting solution is heated at reflux for 1 hour. The solution is diluted with H_2O and extracted with Et_2O . The organic layer is washed with H_2O and saturated $NaCl$ solution, then dried over $MgSO_4$, filtered and concentrated. The crude aldehyde is dissolved in 40 mL of anhydrous MeOH and sodium borohydride (0.85 g, 22.5 mmol) is added portionwise. The mixture is stirred at room temperature for 10 min, then quenched with water. The mixture is diluted with Et_2O and the layers separated. The organic layer is washed with H_2O , then dried over $MgSO_4$, filtered and concentrated to yield the title compound (2.23 g, 9.66 mmol) which is used in the subsequent step without further purification. 1H NMR ($CDCl_3$, 300MHz) δ 6.95 (d, 1H), 6.90 (m, 2H), 6.86 (d, 1H), 4.82 (s, 2H), 1.88 (bs, 1H).

B. 5-Bromomethyl-5'-chloro-[2,2']bithiophenyl.

To a solution of (5'-chloro-[2,2']bithiophenyl-5-yl)-methanol (2.23 g, 9.66 mmol) in 65 mL of CH_2Cl_2 is added bromotrimethylsilane (3.82 mL, 29.0 mmol). After 4 h, the solution is concentrated in vacuo. The crude product is stirred in hot hexanes and filtered. The filtrate is concentrated and the title compound (1.67 g, 5.69 mmol) is obtained as a green solid. 1H NMR ($CDCl_3$, 300MHz) δ 7.00 (d, 1H), 6.94 (m, 2H), 6.85 (d, 2H), 4.71 (s, 2H).

30

EXAMPLE 7. 7-Bromomethyl-4-chloroquinazoline.

A. 7-Methyl-3H-quinazolin-4-one.

A solution of 2-amino-4-methylbenzoic acid (31.6 g, 206 mmol) in formamide (60mL) is heated to 130°C for 1 hour, then at 175°C for 3 hours. The solution is poured into 500 mL of ice

water. The resulting solid is collected by filtration and further dried under reduced pressure. The title compound (26.2 g, 170 mmol) is obtained as a white solid. MS (EI): *m/z* 159 (M⁺).

B. 4-Chloro-7-methyl-quinazoline.

To a solution of 7-methyl-3H-quinazolin-4-one (10.6 g, 69 mmol) in toluene (350mL) is added triethylamine (17.5 g, 173 mmol) followed by phosphorous oxychloride (12.3 g, 80 mmol). The resulting solution is heated to 80°C. After 4 hours, the solution is cooled to ambient temperature. The reaction mixture is poured into 500 mL of water. The layers are separated and the organic layer is washed with H₂O, saturated NaHCO₃, and saturated NaCl, dried over MgSO₄, filtered and concentrated. The resulting crude product is purified by recrystallization from EtOAc. The title compound is obtained as a white solid (10g, 56 mmol).

¹H NMR (CDCl₃, 300 MHz) δ 9.02 (s, 1H), 8.16 (d, 1H), 7.87 (s, 1H), 7.55 (d, 1H), 2.62 (s, 3H).

C. 7-Bromomethyl-4-chloroquinazoline.

To a solution of 4-chloro-7-methylquinazoline (7.0 g, 39 mmol) in carbon tetrachloride (140 mL) is added N-bromosuccinimide (8.0 g, 45 mmol), and benzoyl peroxide (0.8 g, 3.3 mmol). The solution is refluxed for 8 hours. After this time, the solution is filtered. The filtrate is concentrated and the residue is stirred with ether to give the title compound as an off-white solid (5.1 g, 20 mmol). ¹H NMR (CDCl₃, 300 MHz) δ 9.10 (s, 1H), 8.30 (d, 1H), 8.10 (s, 1H), 7.82 (d, 1H), 4.68 (s, 2H). MS (EI): *m/z* 237 (M⁺).

EXAMPLE 8. 3-Bromomethyl-7-chloro-1H-quinolin-2-one.

A. N-(3-Chlorophenyl)-2-methyl-3-phenylacrylamide.

To a solution of 3-chloroaniline (0.98 mL, 9.3 mmol) in CH₂Cl₂ (25 mL) at 0°C is added pyridine (0.78mL, 9.5 mmol). To the resulting solution is added dropwise a solution of α-methyl cinnamic acid chloride (1.6 g, 9.3 mmol) in CH₂Cl₂ (8 mL). After 3 hours, the solution is concentrated. The crude product is purified by column chromatography eluting with 5%EtOAc/hexanes to 10%EtOAc/hexanes. The title compound is obtained as a solid (2.5 g, 9.2 mmol). ¹H NMR (CDCl₃, 300 MHz) δ 7.95 (m, 1H), 7.73 (s, 1H), 7.46 (m, 1H), 7.33 (m, 6H), 7.22 (m, 1H), 7.03 (m, 1H), 2.13 (s, 3H).

B. 7-Chloro-3-methyl-1H-quinolin-2-one.

To a solution of N-(3-chlorophenyl)-2-methyl-3-phenylacrylamide (2.5 g, 9.2 mmol) in chlorobenzene (50 mL) is added AlCl₃ (6.2 g, 46 mmol). The solution is heated to 120°C. After 4 hours, the solution is poured onto ice. The solution is filtered. The organic layer is washed with 1N HCl, H₂O and saturated NaCl. The crude product is purified by column chromatography eluting with 2% MeOH/CH₂Cl₂. The title compound is obtained as a white solid

(1.5 g, 7.74 mmol). ^1H NMR (d₆-DMSO, 300 MHz) δ 11.82 (bs, 1H), 7.73 (s, 1H), 7.52 (m, 1H), 7.21 (m, 2H), 2.08 (s, 3H).

C. 3-Bromomethyl-7-chloro-1H-quinolin-2-one.

The title compound is prepared as described in Example 7, Part C, substituting 7-chloro-

5 3-methyl-1H-quinoline-2-one for 7-methyl-4-chloroquinazoline. The title compound is obtained as a white solid. ^1H NMR (d₆-DMSO, 300 MHz) δ 12.00 (bs, 1H), 8.17 (s, 1H), 7.72 (d, 1H), 7.29 (m, 2H), 4.58 (s, 2H).

EXAMPLE 4. 6-Bromomethyl-2-chloro-quinoline.

10 A. 6-Methyl-1H-quinolin-2-one.

The title compound is prepared from p-toluidine and cinnamoyl chloride according to the procedure described in Synthesis 1975, 739. The crude product obtained is triturated in Et₂O/hexanes and filtered to give the title compound as a beige solid. ^1H NMR (DMSO-d₆, 300 MHz) δ 11.60 (bs, 1H), 7.82 (d, 1H), 7.41 (s, 1H), 7.30 (d, 1H), 7.18 (d, 1H), 6.45 (d, 1H), 2.30 (s, 3H).

15 B. 2-Chloro-6-methylquinoline.

6-Methyl-1H-isoquinolin-2-one (14.6 g, 91.7 mmol) in phosphorus oxychloride (160 mL) is heated at 60°C for 17 hours. The mixture is cooled to room temperature, then concentrated to a beige residue. The residue is diluted with ice water and the pH is adjusted to about 8 by slow addition of 10 N NaOH. The crude product is precipitated out during neutralization of the aqueous solution and the solid is filtered, washed with water and dried. The solid is recrystallized from MeOH to afford the title compound (12.0 g, 67.5 mmol) as a beige solid. ^1H NMR (CDCl₃, 300 MHz) δ 8.02 (d, 1H), 7.92 (d, 1H), 7.60 (s, 1H), 7.58 (d, 1H), 7.33 (d, 1H), 2.53 (s, 3H).

25 C. 6-Bromomethyl-2-chloro-quinoline.

N-Bromosuccinimide (12.9 g, 72.5 mmol) and benzoyl peroxide (0.33 g, 1.30 mmol) are added to a solution of 2-chloro-6-methyl-quinoline (12.0 g, 67.5 mmol) in carbon tetrachloride (300 mL). The mixture is heated at reflux for 6 hours. At this time, the resulting mixture is cooled to room temperature, filtered, washed with CH₂Cl₂ and concentrated in vacuo. The crude residue is recrystallized from 50% EtOAc/hexanes to yield the title compound (8.80 g, 34.3 mmol) as a beige crystalline solid. ^1H NMR (CDCl₃, 300 MHz) δ 8.08 (d, 1H), 8.02 (d, 1H), 7.83 (s, 1H), 7.77 (dd, 1H), 7.40 (d, 1H), 4.65 (s, 2H). MS (EI): m/z 256, 258 (M⁺), Cl pattern.

EXAMPLE 10. 3-Bromomethyl-1,7-dichloro-2H-isoquinoline.

35 A. 3-(4-Chlorophenyl)-2-methyl-acryloyl azide.

To a solution of 3-(4-chlorophenyl)-2-methyl-acrylic acid (11.2 g, 57 mmol) in 500 mL of acetone at 0°C is added triethyl amine (9.6 mL, 68 mmol) followed by ethyl chloroformate (6.2 mL, 63 mmol). The solution is allowed to warm to ambient temperatures. After 2 h, sodium azide (5.6 g, 86 mmol) in 35 mL of H₂O is added. After addition, the solution is stirred for 2 hours. The solution is diluted with H₂O (100 mL). The resulting solid is collected by filtration giving the title compound as a white solid (11.1 g, 50mmol). ¹H NMR (CDCl₃, 300 MHz) δ 7.67 (s, 1H), 3.38 (m, 4H), 2.10 9s, 3H).

5 **B. 7-Chloro-3-methyl-2H-isoquinoline-1-one.**

3-(4-Chlorophenyl)-2-methyl-acryloyl azide (11.0 g, 50 mmol) is dissolved in 80 mL of diphenyl ether. The solution is added dropwise to a solution of tributyl amine (11.8 mL, 50mmol) in 170 mL of diphenyl ether at 210°C. After 4 hours., the solution is cooled 50°C and diluted with 1.5 L of hexanes. The resulting solid is collected by filtration giving the title compound as a white solid (7.2 g, 37 mmol). ¹H NMR (d6-DMSO, 300 MHz) δ 11.4 (bs, 1H), 8.02 (s, 1H), 7.67 (d, 1H), 7.55 (d, 1H), 6.34 (s, 1H), 2.18 (s, 3H).

15 **C. 1,7-Dichloro-3-methyl-isoquinoline.**

A solution of 7-chloro-3-methyl-2H-isoquinoline-1-one (7.1 g, 36.7 mmol) in 100 mL of phosphorous oxychloride is heated to 100°C. After 5 h, the solution is concentrated to dryness. The residue is dissolved in CH₂Cl₂. The solution is washed with H₂O. The organic layer is dried over MgSO₄, filtered and concentrated. The crude product is purified by column chromatography eluting with a gradient of 3%EtOAc/hexanes to 5% EtOAc/hexanes. The title compound is obtained as a white solid (6.0g, 28 mmol). ¹H NMR (CDCl₃, 300 MHz) δ 8.23 (s, 1H), 7.68 (m, 1H), 7.63 (m, 1H), 7.40 (s, 1H), 2.64 (s, 3H).

20 **D. 3-Bromomethyl-1,7-dichloro-2H-isoquinoline.**

The title compound is prepared as described in Example 7, part C, substituting 1,7-dichloro-3-methyl-isoquinoline for 4-chloro-7-methylquinazoline. ¹H NMR (CDCl₃, 300 MHz) δ 8.29 (s, 1H), 7.82 (m, 1H), 7.76 (m, 2H), 4.68 (s, 2H).

EXAMPLE 11. 3-Bromomethyl-7-chloroisoquinoline.

A. 7-Chloro-3-methyl-isoquinoline.

30 To a solution of 1,7-dichloro-3-methyl-isoquinoline (0.50 g, 2.36 mmol), Example 10, part C, in 5.5 mL of 9:1 acetic acid:H₂O at 75°C is added zinc (0.23 g, 3.54 mmol) After 75 minutes, the solution is cooled to ambient temperatures. The solution is diluted with a 4:1 EtOAc:CH₂Cl₂ solution. To the solution is added 100mL of a 1N NaOH solution. The aqueous solution is extracted with 4:1 EtOAc:CH₂Cl₂. The combined organic layers are washed with a saturated NaCl solution. The organic layer is dried over MgSO₄, filtered and concentrated. The

crude product is purified by column chromatography eluting with a gradient of 5%EtOAc/hexanes to 15% EtOAc/hexanes. The title compound is obtained as a white solid (0.36 g, 1.97 mmol). ^1H NMR (CDCl_3 , 300 MHz) δ 9.09 (s, 1H), 7.89 (s, 1H), 7.61 (d, 1H), 7.55 (d, 1H), 7.44 (s, 1H) 2.68 (s, 3H). MS (EI): m/z 177, 179 (M $^+$), Cl pattern.

5 **B. 3-Bromomethyl-7-chloroisoquinoline.**

The title compound is prepared as described in Example 7, part C, substituting 7-chloro-3-methyl-isoquinoline for 4-chloro-7-methylquinazoline. ^1H NMR (CDCl_3 , 300 MHz) δ 9.18 (s, 1H), 7.97 (s, 1H), 7.75 (m, 2H), 7.67 (m, 1H), 4.71 (s, 2H).

10 **EXAMPLE 12. 2-Bromomethyl-6-chloronaphthalene.**

A. 6-Chloro-3,4-dihydro-1H-naphthalene-2-one.

To a solution of (4-chlorophenyl)-acetyl chloride (17.3 g, 92 mmol) in 50 mL of CH_2Cl_2 at -20°C is added a solution of AlCl_3 (24.4 g, 184 mmol) in 200 mL CH_2Cl_2 dropwise. After 20 minutes, ethylene (g) is bubbled through the solution for 30 minutes. The solution is stirred at -10°C for 15 minutes. The reaction mixture is poured into 300 g of ice. The layers are separated. The organic layer is washed with H_2O , saturated NaHCO_3 and saturated NaCl . The organic layer is dried over MgSO_4 , filtered and concentrated. The resulting solid is triturated with pentane (2x20mL). The solid is then dried to give the title compound as a solid (15.2 g, 84.2 mmol). ^1H NMR (CDCl_3 , 300 MHz) δ 7.28 (m, 2H), 7.06 (m, 1H), 3.52 (s, 2H), 3.04 (m, 2H), 2.56 (m, 2H).

20 **B. 6-Chloro-2-methyl-1,2,3,4-tetrahydronaphthalene-2-ol.**

To a solution of TiCl_4 (95 mL, 1M in toluene) at -45°C is added a solution of CH_3MgBr (4.2 mL 3M in THF). The solution is stirred for 20 minutes. After this time, 6-chloro-3,4-dihydro-1H-naphthalene-2-one (11.3 g, 63 mmol) in 80 mL of CH_2Cl_2 is added dropwise over 15 minutes. The reaction is stirred for an additional 15 min at -45°C. The solution is warmed to 0°C. After 2 h, the solution is diluted with H_2O and CH_2Cl_2 . The organic layer is dried over MgSO_4 , filtered and concentrated. The title compound is obtained as an oil (11.3 g, 57.5 mmol). ^1H NMR (CDCl_3 , 300 MHz) δ 7.10 (m, 2H), 6.97 (m, 1H), 3.02 (m, 2H), 2.80 (s, 3H), 1.85 (m, 2H), 1.80 (m, 2H).

30 **C. 2-Chloro-6-methyl naphthalene.**

A solution of 6-chloro-2-methyl-1,2,3,4-tetrahydronaphthalene-2-ol (11.3 g, 57.5 mmol) and Ph_3COH (16.5 g, 63 mmol) in 80 mL of TFA is stirred for 2.5 days. After this time, the solution is concentrated to dryness. The residue is dissolved in CH_2Cl_2 . The organic layer is washed with H_2O , saturated NaHCO_3 , and saturated NaCl . The organic layer is dried over MgSO_4 , filtered and concentrated. The crude product is purified by column chromatography

eluting with hexanes. The title compound is obtained as a white solid (4.05 g, 22.9 mmol). ¹H NMR (CDCl₃, 300 MHz) δ 7.78 (s, 1H), 7.69 (m, 2H), 7.58 (s, 1H), 7.50 (m, 2H), 2.49 (s, 3H).

D. 2-Bromomethyl-6-chloronaphthalene.

The title compound is prepared as described in Example 7, part C, substituting 2-chloro-

5 6-methyl naphthalene for 4-chloro-7-methylquinazoline. ¹H NMR (CDCl₃, 300 MHz) δ 7.82 (m, 2H), 7.78 (s, 1H), 7.76 (m, 2H), 7.52 (d, 1H), 7.42 (d, 1H), 4.62 (s, 2H).

EXAMPLE 13. 2-(Benzhydrylidene-amino)-4-bromomethyl-benzonitrile.

A. 2-(Benzhydrylidene-amino)-4-methyl-benzonitrile.

10 To a solution of 2-amino-4-methyl benzonitrile (20 g, 151 mmol) in 1000mL of dichloroethane is added benzophenone imine (30g, 166mmol). The solution is refluxed for 48 hours. After this time, the solution is cooled to ambient temperatures. The solution is washed with sat. NaHCO₃, water and sat. NaCl. The organic layer is dried over MgSO₄, filtered and concentrated under vacuum. The product is further purified by recrystallization from t-butyl ether. The title compound (25.5g, 118mmol) is obtained as a yellow solid. ¹H NMR (CDCl₃, 300MHz) δ 7.88 (m, 2H), 7.42 (m, 3H), 7.32 (m, 7H), 6.79 (d, 1H), 6.58 (s, 1H), 2.23 (s, 3H).

B. 2-(Benzhydrylidene-amino)-4-bromomethyl-benzonitrile.

20 To a solution of 2-(benzhydrylidene-amino)-4-methyl-benzonitrile (11.2g, 37.8mmol) in 500mL of CCl₄, is added N-bromosuccinimide (7.06g, 39.7mmol), and benzoyl peroxide (0.92g, 3.8mmol). The solution is heated to reflux for 16 hours. After this time, the solution is filtered and the organic solution is concentrated under vacuum. The residue is purified by column chromatography eluting with a gradient of 20%t-butyl ether/hexanes to 25% t-butyl ether/hexanes. The product is obtained as an oil containing a mixture of the desired monobromide, dibromide and unreacted starting material. The mixture is assayed by proton NMR and is found to have a purity between 60-75%. ¹H NMR (CDCl₃, 300MHz) δ 7.82 (m, 2H), 7.42 (m, 9H), 6.92 (d, 1H), 6.81 (s, 1H), 4.29 (s, 2H).

EXAMPLE 14. 7-Bromomethyl-4-chloroquinoline.

A. 7-Methyloxycarbonyl-4-chloroquinoline.

30 4-Chloro-7-trifluoromethylquinoline (5.0 g, 21.6 mmol) in 100 mL 80% H₂SO₄ is heated to 200°C for 24 hours in a sealed tube. The solution is cooled, poured into water and neutralized with sodium hydroxide to pH ~ 3-4. The precipitated solid is collected, washed with water and dissolved in 2 N sodium hydroxide. The aqueous solution is washed with ethyl acetate then acidified to pH~3-4. The precipitate is collected, washed with water and dried in a vacuum oven overnight to yield 7-carboxy-4-chloroquinoline as a solid (5.1 g, 24.6 mmol). A portion of this material (2.0 g, 9.6 mmol) is treated with anhydrous THF (200 mL) and DMF (2

mL) and 2 M oxalyl chloride in methylene chloride (14.5 mL, 29 mmol). The resulting suspension is stirred at room temperature for 2 h then treated with methanol (10 mL). After stirring 30 minutes the solution is concentrated and the residue is taken up in methylene chloride. The solution is washed with saturated sodium bicarbonate and dried (sodium sulfate) and concentrated to yield the title compound as a solid (2.1 g, 9.5 mmol). MS m/z: M⁺ = 221; ¹H NMR (CDCl₃, 300 MHz) δ 8.6 (s, 1H), 8.2 (s, 1H), 7.9 (d, 1H), 7.65 (d, 1H), 7.45 (s, 1H), 3.95 (s, 3H).

5 **B. 7-Hydroxymethyl-4-chloroquinoline.**

7-Methyloxycarbonyl-4-chloroquinoline (2.1 g, 9.5 mmol) is dissolved in anhydrous THF (25 mL) and anhydrous ether (200 mL). The solution is cooled in a dry ice/acetone bath and treated 1M lithium aluminum hydride in THF (11.0 mL, 11 mmol). The solution is warmed (approximately -45°C) for 20 minutes and quenched with ethyl acetate. The solution is diluted with ether (100 mL) and treated with water (36 mL), 15% NaOH (36 mL) and water (36 mL) in succession. The mixture is filtered and evaporated to yield the title compound as a residue (2.0 g, 9.7 mmol) which is dried under vacuum and used without further purification. MS m/z: M⁺ = 193; ¹H NMR (CDCl₃, 300 MHz) δ 8.65 (d, 1H), 8.15 (d, 1H), 8.0 (d, 1H), 7.6 (d, 1H), 7.45 (d, 1H), 4.8 (s, 2H).

10 **C. 7-Bromomethyl-4-chloroquinoline.**

7-Hydroxymethyl-4-chloroquinoline (0.2 g, 0.97 mmol) is treated with 48 % HBr and heated to 120°C for 1 hours. The resulting solution is cooled with ice, diluted with water and treated with ethyl acetate and sodium bicarbonate until basic to pH paper. The layers are separated and the organic layer is washed with water, dried (Na₂SO₄) and concentrated to give 7-bromomethyl-4-chloroquinoline (0.23 g, 0.9 mmol). MS m/z: M⁺ = 255; ¹H NMR (CDCl₃, 300 MHz) δ 8.75 (d, 1H), 8.25 (d, 1H), 8.1 (s, 1H), 7.7 (d, 1H), 7.5 (d, 1H), 4.7 (s, 2H).

15

EXAMPLE 15. 7-Bromomethyl-4-chlorocinnoline.

A. 4-methyl-2-nitrophenylethanone.

4-Fluoro-3-nitrotoluene (7.5 g, 48.4 mmol) is treated with a solution of nitroethane (15.2 mL, 200 mmol) in ethyl acetate (100 mL) and DBU (21 mL, 145 mmol) and stirred overnight at ambient temperature. The solution is concentrated under vacuum, diluted with methanol, treated with 30% H₂O₂ (25 mL) and 10% sodium bicarbonate (25 ml) and stirred overnight at ambient temperature. The reaction mixture is concentrated in vacuo, acidified with 5% HCl and extracted with methylene chloride. The organic layer is dried (sodium sulfate) and chromatographed (35% ethyl acetate/hexane) to give the title compound (7.2 g, 40.2 mmol).

MS m/z: M⁺ = 279; ¹H NMR (CDCl₃, 300MHz) δ 7.8 (s, 1H), 7.48 (d, 1H), 7.32 (d, 1H), 2.5 (s, 3H), 2.4 (s, 3H).

B. 2-Amino-4-methylphenylethanone.

A solution of 4-methyl-2-nitrophenylethanone (5.0 g, 28 mmol) in methanol (100 mL) is treated with ammonium formate (9.6 g, 140 mmol) and 5% palladium on carbon (1.5 g). The mixture is heated to 60°C for 6 h then stirred at ambient temperature for 16 hours. The reaction mixture is filtered through Celite and the filtrate is concentrated in vacuo. The concentrate is treated with sodium bicarbonate and partitioned between water and ethyl acetate. The organic layer is separated, dried with sodium sulfate and concentrated to give crude title compound (4.5 g, 30.2 mmol) which is used without further purification. MS m/z:M⁺ = 149; ¹H NMR (CDCl₃, 300MHz) δ 8.05 (d, 1H), 7.4 (d, 1H), 7.25 (s, 1H), 2.8 (s, 3H), 2.45 (s, 3H).

C. 7-Methyl-1-H-cinnolin-4-one.

A solution of 2-amino-4-methylphenylethanone (5.0 g, 33.6 mmol) in concentrated HCl (100 mL) is treated, in portions, with a solution of sodium nitrite (5.7 g, 82.6 mmol) in water (~ 10 mL). The resulting solution is stirred at 60°C for 2 hr, cooled to ambient temperature and diluted with a saturated solution of sodium acetate (~ 200 mL). Solid sodium acetate is added portionwise until the solution tested basic to pH paper. Upon stirring, the title compound precipitated as a white solid which is collected and air dried (2.3 g, 14.3 mmol). MS m/z: [M+H]⁺ = 161; ¹H NMR (CDCl₃, 300MHz) δ 8.1 (d, 1H), 7.85 (s, 1H), 7.45 (s, 1H) 7.3 (d, 1H), 2.55 (s, 3H).

D. 4-Chloro-7-methylcinnoline.

7-Methyl-1-H-cinnolin-4-one (1.3 g, 8.1 mmol) is treated with about 80 mL of chlorobenzene and heated until the solid dissolves. The resulting solution is cooled and treated with pyridine (0.16 mL, 2 mmol) and POCl₃ (1.13 mL, 12.2 mmol). The solution is heated to reflux for 1 h then concentrated to dryness. The residue is chromatographed (20 % ethyl acetate/hexane) to yield the title compound as a tan solid (~ 1 g, 5.6 mmol). MS m/z (M+=178); ¹H NMR (CDCl₃, 300MHz) δ 9.3 (s, 1H), 8.35 (s, 1H), 8.1 (d, 1H), 7.7 (d, 1H), 2.68 (s, 3H).

E. 7-Bromomethyl-4-chlorocinnoline.

A solution of 4-chloro-7-methylcinnoline (0.6 g, 3.37 mmol) in carbon tetrachloride (30 mL) is treated with N-bromosuccinimide (0.64 g, 3.4 mmol) and a catalytic amount of 70 % benzoyl peroxide (0.22 g, 0.63 mmol). The solution is heated to 80 °C overnight, then filtered. The filtrate is concentrated in vacuo and the resulting residue is chromatographed (20 % ethyl acetate/ methyl chloride) to give the title compound (0.3 g, 1.2 mmol) and some unreacted

starting material (0.1 g, 0.56 mmol). MS m/z: [M+H]⁺ = 257; ¹H NMR (CDCl₃, 300MHz) δ 9.35 (s, 1H), 8.55 (s, 1H), 8.2 (d, 1H), 8.85 (d, 1H), 4.75 (s, 2H).

EXAMPLE 16. 6-Bromomethyl-3-chloro-1-(toluene-4-sulfonyl)-1H-indole.

5 A. 1H-Indole-6-carboxylic acid methyl ester.

To a solution of 6-indole carboxylic acid (0.91 g, 5.67 mmol) in 33 mL of 2:1 THF/MeOH is added (trimethylsilyl)diazomethane (5.0 mL of a 2.0M solution in hexanes, 10.0 mmol). The mixture is stirred for 3 h and concentrated in vacuo to give the title compound (0.87 g, 4.97 mmol). The crude product is used in the next step without further purification. ¹H NMR (CDCl₃, 300 MHz) δ 8.70 (bs, 1H), 8.20 (s, 1H), 7.82 (dd, 1H), 7.67 (d, 1H), 7.45 (m, 1H), 6.60 (m, 1H), 3.95 (s, 3H).

10 B. 3-Chloro-1H-indole-6-carboxylic acid methyl ester.

15 To a solution of 1H-indole-6-carboxylic acid methyl ester (5.86 g, 33.5 mmol) in 30 mL of CH₂Cl₂ is added N-chlorosuccinimide (0.58, 4.33 mmol) portionwise over 1.5 hours. The mixture is stirred for 2 h, then diluted with water. The layers are separated and the organic phase is washed with water and saturated NaCl solution. The organic layer is dried over MgSO₄, filtered and concentrated in vacuo to give the title compound (5.74 g, 27.3 mmol). The crude product is used in the next step without further purification. ¹H NMR (CDCl₃, 300 MHz) δ 8.46 (bs, 1H), 8.19 (s, 1H), 7.90 (dd, 1H), 7.69 (d, 1H), 7.36 (d, 1H), 3.97 (s, 3H).

20 C. 3-Chloro-1-(toluene-4-sulfonyl)-1H-Indole-6-carboxylic acid methyl ester.

25 To a solution of 3-chloro-1H-indole-6-carboxylic acid methyl ester (3.00 g, 17.1 mmol) in 40 mL of THF at -78°C is added LDA(8.55 mL of a 2.0M solution in hexanes, 17.1 mmol) dropwise. The solution is stirred at -78°C for 30 minutes p-Toluenesulfonyl chloride (3.43 g, 18.0 mmol) in 15 mL of THF is added dropwise and the resulting solution is stirred at -78°C for 3 hours. The mixture is warmed to 0°C, quenched with saturated NaHCO₃ solution and diluted with H₂O and Et₂O. The layers are separated. The organic phase is washed with saturated NaHCO₃ solution, H₂O and saturated NaCl solution, then dried over MgSO₄, filtered and concentrated. The crude residue is purified via flash column chromatography eluting with a gradient of 10% EtOAc/hexanes to 30% EtOAc/hexanes to provide the title compound (3.64 g, 10.0 mmol). ¹H NMR (CDCl₃, 300MHz) δ 8.70 (s, 1H), 8.01 (dd, 1H), 7.80 (d, 2H), 7.70 (s, 1H), 7.60 (d, 1H), 7.38 (m, 2H), 4.00 (s, 3H), 2.49 (s, 3H).

30 D. [3-Chloro-1-(toluene-4-sulfonyl)-1H-indol-6-yl]-methanol.

35 To a solution of 3-chloro-1-(toluene-4-sulfonyl)-1H-Indole-6-carboxylic acid methyl ester (3.10 g, 8.53 mmol) in 50 mL of toluene at -78°C is added DIBAL (13.8 mL of a 1.5M solution in toluene, 20.8 mmol) dropwise. The mixture is stirred at -78°C for 2 h, then warmed to room

temperature and stirred for 2 hours. The reaction mixture is quenched by the addition of MeOH and washed with saturated disodium tartrate solution. The aqueous layer is extracted with Et₂O. The combined organics are washed with saturated disodium tartrate solution, water and saturated NaCl solution. The organic phase is then dried over anhydrous MgSO₄, filtered and concentrated to give the title compound (2.88 g). The crude product is used in the next step without further purification. ¹H NMR (CDCl₃, 300 MHz) δ 8.01 (s, 1H), 7.79 (d, 2H), 7.56 (s, 1H), 7.53 (d, 1H), 7.31 (d, 1H), 7.25 (d, 2H), 4.84 (s, 2H), 2.37 (s, 3H), 1.88 (bs, 1H).

5 **E. 6-Bromomethyl-3-chloro-1-(toluene-4-sulfonyl)-1H-indole.**

To a solution of [3-chloro-1-(toluene-1-sulfonyl)-1H-indol-6-yl]-methanol (0.45 g, 1.34 mmol) in 13 mL of Et₂O at 0°C is added phosphorous tribromide (0.04 mL, 0.40 mmol). The mixture is stirred at 0°C for 15 min, then at room temperature for 2 hours. The mixture is quenched by the addition of water/ice and diluted with Et₂O. The layers are separated and the organic phase is washed with saturated NaHCO₃ solution, water and saturated NaCl solution. The organic layer is dried over anhydrous MgSO₄, filtered and concentrated to provide the title compound (0.47 g, 1.18 mmol) as an oil. The crude product is used in the subsequent step without further purification. ¹H NMR (CDCl₃, 300 MHz) δ 8.09 (s, 1H), 7.79 (d, 2H), 7.59 (s, 1H), 7.50 (d, 1H), 7.35 (d, 1H), 7.27 (m, 2H), 4.66 (s, 2H), 2.39 (s, 3H).

20 **EXAMPLE 17. 2-(3-Bromo-(E)-propenyl)-5-chloro-thiophene.**

A. 3-(5-Chloro-thiophen-2-yl)-(E)-acrylic acid methyl ester.

To a solution of 5-chloro-2-thiophene-carboxaldehyde (5.10 g, 34.8 mmol) in 100 mL of dry CH₂Cl₂ is added methyl (triphenylphosphoranylidene)acetate (11.8 g, 35.3 mmol). The resulting brown-green mixture is stirred for 19 h at room temperature. The mixture is filtered through a Celite pad, concentrated in vacuo and triturated with hexane. The white precipitate (triphenylphosphine oxide) is filtered off and the filtrate is concentrated. The crude residue is purified via flash column chromatography eluting with a gradient of 5% EtOAc/hexanes to 10% EtOAc/hexanes to provide the title compound (6.20 g, 30.6 mmol) as a yellow solid. ¹H NMR (CDCl₃, 300MHz) δ 7.65 (d, 1H), 7.05 (d, 1H), 6.89 (d, 1H), 6.10 (d, 1H), 3.80 (s, 3H).

25 **B. 3-(5-Chloro-thiophen-2-yl)-prop-2-(E)-en-1-ol.**

30 To a solution of 3-(5-chloro-thiophen-2-yl)-(E)-acrylic acid methyl ester (5.00 g, 24.7 mmol) in 80 mL of CH₂Cl₂ at 0°C is added slowly a solution of DIBAL (36.2 mL of a 1.5M solution in toluene, 54.3 mmol). The mixture is stirred at 0°C for 15 min, then quenched by the addition of 6 mL of MeOH. The mixture is allowed to warm to room temperature, diluted with water/ice and stirred for 15 minutes. The mixture is filtered through a pad of Celite and washed with CH₂Cl₂. The layers are separated and the aqueous layer is extracted with CH₂Cl₂. The

combined organics are washed with saturated NaCl solution, dried over anhydrous Na₂SO₄, filtered and concentrated. The residue is purified via flash column chromatography eluting with a gradient of 15% EtOAc/hexanes to 25% EtOAc/hexanes to afford the title compound (4.18 g, 23.9 mmol) as an oil. ¹H NMR (CDCl₃, 300 MHz) δ 6.77 (d, 1H), 6.71 (d, 1H), 6.60 (d, 1H), 6.10 (m, 1H), 4.30 (d, 2H), 1.79 (bs, 1H).

5 C. 2-(3-Bromo-(E)-propenyl)-5-chloro-thiophene.

To a solution of 3-(5-chloro-thiophen-2-yl)-prop-2-(E)-en-1-ol (4.18 g, 23.9 mmol) in 140 mL of Et₂O at 0°C is added phosphorous tribromide (1.34 mL, 14.3 mmol) in 10 mL of Et₂O. The mixture is stirred at 0°C for 45 min, then at room temperature for 1.5 hours. The mixture is 10 quenched by the addition of water/ice and diluted with Et₂O. The layers are separated and the organic phase is washed with water until neutral (3x) and once with saturated NaCl solution. The organic layer is dried over anhydrous MgSO₄, filtered and concentrated to provide the title compound (5.46 g, 23.0 mmol) as an oil. The crude material solidified upon storage in the freezer and can be used in the subsequent step without further purification. ¹H NMR (CDCl₃, 15 300 MHz) δ 6.80 (m, 2H), 6.65 (d, 1H), 6.10 (m, 1H), 4.10 (d, 2H).

EXAMPLE 18. 3-(4-Bromo-furan-2-yl)-(E)-propenal.

To a solution of 4-bromo-2-furfuraldehyde (0.5 g, 2.86 mmol) in 30 mL of dry CH₂Cl₂ is 20 added (triphenylphosphoranylidene)acetaldehyde (0.87 g, 2.86 mmol). The resulting mixture is stirred for 16 h at room temperature. The crude mixture is concentrated in vacuo and the residue is purified via flash column chromatography eluting with CH₂Cl₂ to provide the title compound (0.15 g, 0.75 mmol) as a white solid. ¹H NMR (CDCl₃, 300 MHz) δ 9.62(d, 1H), 7.59 (s, 1H), 7.18 (d, 1H), 6.81 (s, 1H), 6.60 (m, 1H).

25 EXAMPLE 19. Acetic acid 3-(6-methoxy-pyridin-3-yl)-(E)-allyl ester.

To a solution of 3-(6-methoxy-pyridin-3-yl)-prop-2-(E)-en-1-ol (0.39 g, 2.36 mmol, prepared as described in EXAMPLE 17 from 6-methoxy-pyridine-3-carbaldehyde (J. Org. Chem. 1990, 72)) in 8 mL of CH₂Cl₂ at 0°C is added triethylamine (0.66 mL, 4.72 mmol), DMAP (0.05 g, 0.40 mmol) and Ac₂O (0.33 mL, 3.54 mmol). The mixture is stirred at 0°C for 45 min, 30 then at room temperature for 16 hours. The mixture is diluted with Et₂O and washed with 1N HCl, water, saturated NaHCO₃ solution and saturated NaCl solution. The organic layer is dried over anhydrous MgSO₄, filtered and concentrated. The residue is purified via flash column chromatography eluting with a gradient of 10% EtOAc/hexanes to 20% EtOAc/hexanes to afford the title compound (0.25 g, 1.21 mmol) as an oil. ¹H NMR (CDCl₃, 300 MHz) δ 8.12 (d,

1H), 7.68 (dd, 1H), 6.72 (d, 1H), 6.60 (d, 1H), 6.18 (dt, 1H), 4.73 (d, 2H), 3.95 (s, 3H), 2.10 (s, 3H).

EXAMPLE 20. 2-(3-Bromo-prop-1-ynyl)-5-chloro-thiophene.

5 **A. 3-(5-Chloro-thiophen-2-yl)-prop-2-yn-1-ol.**

Nitrogen (g) is bubbled through a solution of 5-bromo-2-chloro-thiophene (1.00 g, 5.06 mmol) in 8 mL of piperidine. After 5 min, propargyl alcohol (0.32 mL, 5.56 mmol), tetrakis(triphenylphosphine) palladium(0) (0.06 g) and CuI (catalytic amount) are added to the solution. The mixture is heated at 80°C for 1 h in a sealed glass vessel. At this time, the 10 mixture is cooled and diluted with EtOAc/Et₂O. The organic layer is washed 3N HCl, water, saturated NaHCO₃ solution and saturated NaCl solution. The organic layer is dried, filtered and concentrated. The crude residue is purified via flash column chromatography eluting with a gradient of 10% EtOAc/hexanes to 20% EtOAc/hexanes to give the title compound (0.8 g, 0.46 mmol) as an oil. ¹H NMR (DMSO-d₆, 300 MHz) δ 6.99 (d, 1H), 6.80 (d, 1H), 4.49 (s, 2H), 1.90 (bs, 1H). EI MS, [M]⁺=172, 174 (Cl pattern).

15 **B. 2-(3-Bromo-prop-1-ynyl)-5-chloro-thiophene.**

The title compound is prepared as described in EXAMPLE 17, Part C, using 3-(5-chloro-thiophen-2-yl)-prop-2-yn-1-ol in place of 3-(5-chloro-thiophen-2-yl)-prop-2-(E)-en-1-ol. The crude product is used in the subsequent step without further purification.

20 ¹H NMR (CDCl₃, 300 MHz) δ 7.04 (d, 1H), 6.80 (d, 1H), 4.98 (d, 2H).

EXAMPLE 21. 2-Bromomethyl-5-chloro-indole-1-carboxylic acid tert-butyl ester.

A. 5-Chloro-2-methyl-indole-1-carboxylic acid tert-butyl ester.

A solution containing 5-chloro-2-methylindole (4.0 g, 24.1 mmol) and DMAP (295 mg, 25 2.42 mmol) in anhydrous THF (100 mL) is cooled to 0°C. A solution containing (Boc)₂O (5.27 g, 24.1 mmol) in anhydrous THF (100 mL) is then added over a 20 min period. The reaction mixture is stirred for 2 h at 0°C and then at ambient temperature for 16 hours. The reaction mixture is concentrated and the crude residue is purified by flash silica gel chromatography (2% EtOAc/hexane to 5% EtOAc/hexane) to provide 5.2 g (81%) of title compound as a pale yellow 30 solid. ¹H NMR (300 MHz, CDCl₃) δ 1.67 (s, 9H), 2.57 (s, 3H), 6.24 (t, J = 0.9 Hz, 1H), 7.16 (dd, J = 8.8, 2.1 Hz, 1H), 7.38 (d, J = 2.1 Hz, 1H), 8.01 (d, J = 8.8 Hz, 1H) ppm; MS (EI): m/z 265 (M⁺).

B. 2-Bromomethyl-5-chloro-indole-1-carboxylic acid tert-butyl ester.

A solution containing 5-chloro-2-methyl-indole-1-carboxylic acid tert-butyl ester (3.0 g, 35 11.3 mmol), NBS (1.33 g, 11.3 mmol), and benzoyl peroxide (0.4 g, 1.13 mmol) in CCl₄ (100

mL) is heated at 80°C for 3 hours. An additional portion of NBS (0.65 g, 5.65 mmol), and benzoyl peroxide (0.2 g, 0.56 mmol) is then added and the reaction mixture is heated for an additional 3 hours. After cooling to ambient temperature, the reaction mixture is filtered. The filtrate is concentrated to a brown oil which is triturated with hexane to remove residual 5 succinimide, filtered, and concentrated. The resultant oil (4.5 g, >100%) is used directly in the next reaction without further purification. ^1H NMR (300 MHz, CDCl_3) δ 1.72 (s, 9H), 4.88 (s, 2H), 6.63 (s, 1H), 7.27 (dd, J = 9.0, 2.0 Hz, 1H), 7.46 (d, J = 2.0 Hz, 1H), 8.09 (d, J = 9.0 Hz, 1H) ppm; MS (EI): m/z 343 (M $^+$).

10 **EXAMPLE 22. 3-Bromomethyl-5-iodo-2-methoxy-pyridine**

A. **5-Iodo-3-methyl-2-methoxy-pyridine.**

To a solution containing 2-bromo-5-iodo-3-methyl-pyridine (4.80 g, 16.0 mmol) in DMSO (15 mL) is added methanolic NaOMe (3.33 M, 5.3 mL, 17.7 mmol) at 0 °C. The solution is allowed to warm to ambient temperature and then heated at 70°C for 1 hour. The reaction 15 mixture is diluted with diethyl ether (300 mL) and water (200 mL) and the layers are separated. The organic phase is washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated. The crude product is purified by silica gel flash column chromatography (hexane/diethyl ether, 19:1) to provide 2.86 g (71%) of the title compound as a white solid. ^1H NMR (300 MHz, CDCl_3) δ 2.12 (s, 3H), 3.90 (s, 3H), 7.60 (d, J = 2.1 Hz, 1H), 8.14 (d, J = 2.1 20 Hz, 1H) ppm; MS (EI): m/z 249 (M $^+$).

B. **3-Bromomethyl-5-iodo-2-methoxy-pyridine.**

A solution containing 5-iodo-3-methyl-2-methoxy-pyridine (1.00 g, 4.00 mmol) and NBS (0.78 g, 4.40 mmol) in CCl_4 (20 mL) is warmed to reflux. AIBN is added in 5 mg portions (0.03 mmol) every hour. After 3 h, the reaction mixture is cooled and then concentrated in vacuo. 25 The residue is dissolved in EtOAc (150 mL) and washed successively with aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (100 mL), water (100 mL), brine then dried over anhydrous Na_2SO_4 , filtered and concentrated. The crude product is purified by silica gel flash column chromatography (hexane/diethyl ether, 19:1) to provide 0.72 g (55%) of the title compound as a white solid. ^1H NMR (300 MHz, CDCl_3) δ 3.97 (s, 3H), 4.38 (s, 2H), 7.83 (d, J = 2.2 Hz, 1H), 8.27 (d, J = 2.2 Hz, 1H) ppm; MS 30 (EI): m/z 327 (M $^+$).

EXAMPLE 23. 5-Bromomethyl-6-methoxy -nicotinic acid methyl ester.

A. **6-Methoxy-5-methyl-nicotinic acid methyl ester.**

A solution containing 5-iodo-3-methyl-2-methoxy-pyridine (10.0 g, 40.0 mmol), Et_3N (8.0 35 g, 80.0 mmol), and $(\text{Ph}_3\text{P})_4\text{PdCl}_2$ (2.80 g, 4.00 mmol) in 1:1 DMF/MeOH (100 mL) is cooled to

0°C. Carbon monoxide is bubbled into the cooled solution for approx. 5 min at which time the reaction mixture is sealed under a balloon of CO. The reaction mixture is allowed to warm to ambient temperature and then stirred for 16 hours. The reaction mixture is concentrated in vacuo and the residue is partitioned between water (300 mL) and EtOAc (300 mL) and the layers are separated. The organic phase is washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The crude product is purified by silica gel flash column chromatography (hexane/diethyl ether, 19:1) to provide 4.10 g (57%) of the title compound as a white solid. ¹H NMR (300 MHz, CDCl₃) δ 2.20 (s, 3H), 3.88 (s, 3H), 4.00 (s, 2H), 7.96 (d, J = 2.2 Hz, 1H), 8.65 (d, J = 2.2 Hz, 1H) ppm; MS (ISP loop): m/z 182 (M+H).

10 **B. 5-Bromomethyl-6-methoxy-nicotinic acid methyl ester.**

A solution containing 6-methoxy-5-methyl-nicotinic acid methyl ester (4.00 g, 22.1 mmol), NBS (5.11 g, 28.7 mmol), and AIBN (0.90 g, 5.5 mmol) in CCl₄ (100 mL) is warmed to reflux. After 5 h, the reaction mixture is cooled and then concentrated in vacuo. The residue is dissolved in EtOAc (500 mL) and washed successively with aqueous Na₂S₂O₃ (300 mL), water (100 mL), brine then dried over anhydrous Na₂SO₄, filtered and concentrated. The crude product is purified by silica gel flash column chromatography (hexane/diethyl ether, 9:1) to provide 3.10 g (54%) of the title compound as a white solid. ¹H NMR (300 MHz, CDCl₃) δ 3.90 (s, 3H), 4.07 (s, 3H), 4.46 (s, 2H), 8.19 (d, J = 2.2 Hz, 1H), 8.79 (d, J = 2.2 Hz, 1H) ppm; MS (EI): m/z 259 (M+).

20

EXAMPLE 24. 5-Chloro-2-thienyloxyacetic acid.

A. 2-Hydroxy-thiophene.

Thiophene (42g, 500mmol) is dissolved in ether (250mL). To the solution is added n-BuLi (200mL of a 2.5N solution in hexanes, 500mmol) at a rate which maintains a gentle reflux. After addition, the solution is stirred for 0.5 hour. The solution is then cooled to -78°C and triethyl borate (102 g, 700mL) is added dropwise. The solution is stirred for 3 hours. The cold bath is removed and 130mL of a 30% H₂O₂ is added dropwise with rapid stirring. After addition, the solution is allowed to reflux for an additional 20 minutes. The solution is then cooled to 0°C and acidified to pH=3 with 6N HCl. The resulting solution is extracted with ether. The organic solution is washed with 10% ferric ammonium sulfate, water and saturated NaCl. The solution is dried over MgSO₄, filtered and concentrated under vacuum. The title compound (32g, 320mmol) is obtained as an oil. ¹H NMR (CDCl₃, 300MHz) δ 7.60 (m, 1H), 6.35 (m, 1H), 4.12 (d, 2H).

B. Ethyl 2-thienyloxyacetate.

To a solution of 2-hydroxy-thiophene (32g, 320 mmol) in CHCl_3 (500mL) is added ethyl bromoacetate (53.4 g, 320 mmol). To the resulting solution is added a solution containing n- Bu_4NHSO_4 (25g, 74mmol) and NaOH (15.8g, 394 mmol) in water (500mL). After addition, the solution is stirred vigorously using mechanical stirring. The reaction is stirred for 12 hours.

5 After this time, the layers are separated. The aqueous layer is extracted with CHCl_3 . The combined organic layers are washed with water and saturated NaCl. The organic layer is dried over MgSO_4 , filtered and concentrated under vacuum. The resulting crude product is purified by column chromatography eluting with a gradient of 30% CH_2Cl_2 :hexanes to 60% CH_2Cl_2 :hexanes. The title compound (11.5g, 62mmol) is obtained as an oil.

10 $^1\text{H NMR}$ (CDCl_3 , 300MHz) δ 6.68 (dd, 1H), 6.60 (d, 1H), 6.22 (d, 1H), 4.62 (s, 2H), 4.30 (q, 2H), 1.31 (t, 3H).

C. Ethyl 5-chloro-2-thienyloxyacetate.

To a solution of ethyl 2-thienyloxyacetate (1.1g, 5.9mmol) in acetic acid (15mL) is added N-chlorosuccinimide (0.78g, 5.9mmol). The solution is stirred for 1.5 hour. After this time the solution is concentrated. The resulting oil is dissolved in ether and washed with 1N NaOH, water and sat. NaCl. The organic layer is dried over MgSO_4 , filtered and concentrated under vacuum. The title compound (1.26g, 5.7mmol) is obtained as an oil. $^1\text{H NMR}$ (CDCl_3 , 300MHz) δ 6.52 (d, 1H), 6.06 (d, 1H), 4.60 (s, 2H), 4.24 (q, 2H), 1.31 (t, 3H).

D. 5-Chloro-2-thienyloxyacetic acid.

20 To a solution of ethyl 5-chloro-2-thienyloxyacetate (0.39g, 1.77mmol) in 9mL of a 1:1:1 mixture of CH_3OH :THF:water is added LiOH (0.38g, 9.0 mmol). The solution is stirred for 16 hours. After this time, the solution is concentrated to 1/3 its volume. The resulting solution is acidified to pH=3 with 1N HCl. The aqueous solution is extracted with CH_2Cl_2 . The organic layer is dried over MgSO_4 , filtered and concentrated under vacuum. The title compound (0.32g, 25 1.66mmol) is obtained as a white solid. $^1\text{H NMR}$ (CDCl_3 , 300MHz) δ 6.50 (d, 1H), 6.07 (d, 1H), 4.66 (s, 2H).

EXAMPLE 25. 3-(5-Chloro-thiophen-2-yl)-(E)-acrylic acid.

30 To a mixture of 3-(5-chloro-thiophen-2-yl)-(E)-acrylic acid methyl ester (0.60 g, 2.96 mmol) in 15 mL of 1:1:1 THF/MeOH/ H_2O at 0°C is added lithium hydroxide monohydrate (0.62 g, 14.7 mmol). The mixture is stirred at 0°C for 1 h, then at room temperature for 1 h and concentrated in vacuo. The residue is diluted with EtOAc and washed with 1N HCl. The aqueous layer is extracted with EtOAc and the combined organics are washed with water (2x), dried, filtered and concentrated to provide the title compound (0.54 g, 2.86 mmol) as a white

solid. The crude material can be used in the subsequent step without further purification. ^1H NMR (CDCl_3 , 300MHz) δ 7.65 (d, 1H), 7.05 (d, 1H), 6.90 (d, 1H), 6.10 (d, 1H).

EXAMPLE 26. 3-(4-Chloro-thiophen-2-yl)-(E)-acrylic acid.

5 **A. 4-Chloro-2-thiophene-carboxaldehyde.**

To a solution of 2-thiophene-carboxaldehyde (6.33 g, 56.4 mmol) in 100 mL of CHCl_3 at 0°C is added aluminum trichloride (16.8 g, 126 mmol) portionwise over a few minutes. In a separate vessel, chlorine gas (4.00 g) is bubbled for about 2 min into 100 mL of CCl_4 at 0°C and then added to the former mixture slowly at 0°C. The resulting mixture is stirred at 0°C for 45 min, then allowed to warm to room temperature and stirred overnight. After 16 h, the reaction mixture is poured slowly into 6N HCl at 0°C, then stirred at room temperature for 2 hours. The layers are separated. The aqueous layer is extracted with CHCl_3 . The combined organic layers are washed with H_2O and saturated NaCl solution, then dried over MgSO_4 , filtered and concentrated. The crude product is purified by column chromatography eluting with 10% EtOAc/hexanes to yield the title compound (6.70 g, 45.9 mmol). ^1H NMR (CDCl_3 , 300 MHz) δ 9.87 (s, 1H), 7.64 (s, 1H), 7.63 (s, 1H).

15 **B. 3-(4-Chloro-thiophen-2-yl)-(E)-acrylic acid methyl ester.**

The title compound is prepared as described in EXAMPLE 1, Part A from 4-chloro-2-thiophene-carboxaldehyde. ^1H NMR (CDCl_3 , 300 MHz) δ 7.69 (d, 1H), 7.15 (s, 1H), 7.11 (s, 1H), 6.25 (d, 1H), 3.82 (s, 3H).

20 **C. 3-(4-Chloro-thiophen-2-yl)-(E)-acrylic acid.**

The title compound is prepared as described in EXAMPLE 1, Part B from 3-(4-chloro-thiophen-2-yl)-(E)-acrylic acid methyl ester. ^1H NMR (CDCl_3 , 300 MHz) δ 7.77 (d, 1H), 7.19 (d, 2H), 6.25 (d, 1H).

EXAMPLE 27. (5-Chloro-thiophen-2-yl)-acetic acid.

A. [2-(5-Chloro-thiophen-2-yl)-1-dimethylaminovinyl]phosphonic acid diethyl ester.

To a suspension of sodium hydride (0.25 g, 6.25 mmol, 60% mineral oil dispersion) in 30 10 mL of THF is added slowly a solution of tetraethyl dimethylaminomethylenediphosphonate (2.03 g, 6.14 mmol, prepared according to the procedure described in Psaume, Montury, and Cosmetic Comm. 1982, 12, 415) in 10 mL of THF. After stirring 1 h, a solution of 5-chloro-2-thiophene carboxaldehyde (0.90 g, 6.14 mmol) in 10 mL of THF is added. The resulting mixture is heated at reflux for 1 h, then cooled to room temperature. The reaction mixture is partitioned 35 between Et_2O and water. The organic layer is washed sequentially with 1N HCl, water and

saturated NaCl, then dried over MgSO₄, filtered and concentrated. The crude product is purified via flash column chromatography eluting with a gradient of 40% EtOAc/hexanes to 50% EtOAc/hexanes to afford the title compound (1.52 g, 4.69 mmol) as an oil. ¹H NMR (CDCl₃, 300 MHz) δ 7.20 (d, 1H), 6.95 (d, 1H), 6.82 (d, 1H), 4.15 (m, 4H), 2.62 (s, 6H), 1.60 (t, 6H).

5 B. (5-Chloro-thiophen-2-yl)-acetic acid.

A mixture of [2-(5-chloro-thiophen-2-yl)-1-dimethylaminovinyl]phosphonic acid diethyl ester (1.52 g, 4.69 mmol) and 30 mL of 6N HCl is heated at reflux for 2 hours. After cooling to room temperature, ice water is added and the mixture is partitioned between Et₂O and water. The organic layer is washed with water (2x), dried over MgSO₄, filtered and concentrated to give the title compound (0.62 g, 3.51 mmol) as a brown solid. The crude material can be used in the subsequent step without further purification. ¹H NMR (CDCl₃, 300 MHz) δ 8.30 (bs, 1H), 7.79 (d, 1H), 6.71 (d, 1H), 3.81 (s, 2H).

EXAMPLE 28. 3-(5-Chloro-thiophen-2-yl)-propionic acid.

15 A. 3-(5-Chloro-thiophen-2-yl)-propionaldehyde.

To a mixture of Pd(OAc)₂ (0.12 g, 0.53 mmol), NaHCO₃ (0.52 g, 6.19 mmol) and NaI (0.28 g, 1.87 mmol) in 5 mL of HMPA is added 5-bromo-2-chloro-thiophene (1.00 g, 5.06 mmol) and allyl alcohol (1.03 mL, 15.2 mmol). The mixture is heated to 90°C and stirred for 16 hours. The reaction mixture is cooled to room temperature, diluted with Et₂O and washed with water. The organic layer is dried over MgSO₄, filtered and concentrated in vacuo. The crude residue is purified by flash column chromatography eluting with a gradient of 10% Et₂O/hexanes to 20% Et₂O/hexanes to provide the product (0.18 g, 1.03 mmol) as an oil. ¹H NMR (CDCl₃, 300 MHz) δ 9.81 (s, 1H), 6.71 (d, 1H), 6.58 (d, 1H), 3.07 (t, 2H), 2.81 (t, 2H).

B. 3-(5-Chloro-thiophen-2-yl)-propionic acid.

25 Silver nitrate (117 mg, 0.69 mmol) in 1 mL of H₂O is added to 1.36 mL of 1N NaOH at 0°C and stirred for 5 minutes. To the brown suspension is added 3-(5-chloro-thiophen-2-yl)-propionaldehyde (60 mg, 0.34 mmol) and the resulting mixture is allowed to warm to room temperature over 2 hours. The precipitate is filtered and washed with hot water (2x). The combined aqueous layers are acidified with 6 N HCl and extracted with EtOAc (2x). The combined organic layers are washed with water (2x), then dried over MgSO₄, filtered and concentrated in vacuo to give the title compound (50 mg, 0.26 mmol) as a beige solid. The crude material can be used in the subsequent step without further purification. ¹H NMR (CDCl₃, 300 MHz) δ 6.72 (d, 1H), 6.60 (d, 1H), 3.07 (t, 2H), 2.71 (t, 2H).

35 EXAMPLE 29. 3-Fluorophenoxy-acetic acid.

A. 3-Fluorophenoxy-acetic acid ethyl ester.

To a solution of 3-fluorophenol (1.2g, 11.8mmol) in 20mL of DMF at 0°C is added sodium hydride (0.47g, 10.7mmol). After stirring for 10 minutes Ethyl bromoacetate (1.2g, 10.7mmol) is added dropwise. The reaction is allowed to warm to ambient temperatures and is stirred for 16 hours. To the reaction is added a saturated solution NH₄Cl (aq.). The resulting mixture is diluted with EtOAc and H₂O. The layers are separated. The organic layer is washed with H₂O and a saturated solution NaCl (aq.). The organic layer is dried over MgSO₄, filtered and concentrated to give the product (2g, 10mmol) as an oil. ¹H NMR (CDCl₃, 300MHz) δ 7.22 (m, 1H), 6.65 (m, 3H), 4.61 (s, 2H), 4.27 (q, 2H), 1.24 (t, 3H).

B. 3-Fluorophenoxy-acetic acid.

To a solution of ethyl 3-fluorophenoxy-acetate (2g, 10mmol) in 24mL of a 1:1:1 solution of MeOH:H₂O:THF is added lithium hydroxide monohydrate (2.25g, 54mmol). The solution is stirred for 16 hours. After this time, the solution is concentrated under reduced pressure to 1/3 of its volume. The remaining solution is acidified to pH=3 with 1N HCl (aq.). The aqueous solution is extracted with EtOAc. The organic layer is washed with a saturated solution NaCl (aq.). The organic layer is dried over MgSO₄, filtered and concentrated to give the product (1.65g, 9.7mmol) as a white solid. ¹H NMR (CDCl₃, 300MHz) δ 9.8 (bs, 1H), 7.28 (m, 1H), 6.69 (m, 3H), 4.70 (s, 2H).

EXAMPLE 30. 2-Chloropyrdin-3-ylamino-acetic acid.

To a solution of 3-amino-2-chloropyridine (1.0g, 7.8mmol) in 20mL of MeOH is added glyoxylic acid (0.86mL of a 50% by weight solution in H₂O, 7.8mmol). After stirring for 10 minutes, NaCNBH₃ (1.54 g, 23mmol) is added. The reaction is stirred for 16 hours., then is concentrated under reduced pressure. The resulting residue is dissolved in H₂O. The solution is acidified to pH=3 with 1N HCl (aq.). The solution is extracted with EtOAc/CH₂Cl₂ (2:1). The organic layer is dried over MgSO₄, filtered and concentrated. The resulting product is obtained as a white solid (0.95g, 5.1mmol). ¹H NMR (d6-DMSO, 300MHz) δ 12.7 (bs, 1H), 7.62 (m, 1H), 7.44 (m, 1H), 6.90 (m, 1H), 5.8 (bs, 1H), 3.95 (AB, 2H).4.70 (s, 2H).

EXAMPLE 31. 5-Chlorothiophen-2-yl-sulfanyl acetic acid.A. Thiophen-2-yl-sulfanyl acetic acid ethyl ester.

To a solution of thiophene-2-thiol (1.49g, 116mmol) in 40mL of CH₃CN is added ethyl bromoacetate (2.14g, 167mmol) followed by K₂CO₃ (3.54g, 138mmol). The solution is stirred for 16 hours. After this time, the solution is filtered. The solvent is evaporate to give the

product as an oil (2.4g, 118mmol). ^1H NMR (CDCl_3 , 300MHz) δ 7.37 (m, 1H), 7.21 (m, 1H), 6.94 (m, 1H), 4.15 (q, 2H), 3.48 (s, 2H), 1.20 (t, 3H). MS (EI): m/z 202 (M+).

B. 5-Chlorothiophen-2-yl sulfanyl acetic acid.

To a solution of thiophen-2-yl-sulfanyl acetic acid ethyl (0.52g, 2.6mmol) in 25 mL of CH_2Cl_2 is added N-chlorosuccinimide (0.35g, 2.6mmol). The solution is stirred for 10 minutes. After this time, 1 drop of TFA is added. The solution is stirred for 16 hours. The reaction mixture is then diluted with 25 mL of CH_2Cl_2 . The resulting solution is washed with 1N NaOH and a saturated NaCl solution. The organic layer is dried over MgSO_4 , filtered and concentrated. The resulting product is obtained as an oil which is determined to contain 45% of the desired product. The oil is then dissolved in 60 mL of 1:1:1 THF:MeOH: H_2O . To the solution is added lithium hydroxide monohydrate (1.26g, 30mmol). The solution is stirred for 16 hours. After this time, the solution is acidified to pH=3 with 1N HCl. The aqueous solution is washed with H_2O and saturated NaCl solution. The solution is extracted with EtOAc/ CH_2Cl_2 (2:1). The organic layer is dried over MgSO_4 , filtered and concentrated. The resulting crude product is purified by column chromatography eluting with 20% MeOH:Et₂O to give the product as a white solid (0.4g, 1.9mmol). MS (EI): m/z 208, 210 (M+), Cl pattern.

EXAMPLE 32. 5'-Chloro-[2,2']bithiophenyl-5-carboxylic acid.

A. 5'-Chloro-[2,2']bithiophenyl-5-carbaldehyde.

To a solution of 5-chloro-[2,2']bithiophene (1.06 g, 5.28 mmol) in 12 mL of THF at -78°C is added n-BuLi (4.4 mL of a 1.6M solution in hexanes, 6.99 mmol). After 15 minutes, DMF (0.97 mL, 14 mmol) is added and the resulting solution is allowed to warm to 0°C. After 15 min, the solution diluted with EtOAc and quenched with saturated NaHCO_3 solution. The organic solution is washed with H_2O and saturated NaCl solution, then dried over MgSO_4 , filtered and concentrated. The crude product is purified by flash column chromatography eluting with a gradient of 10% Et₂O/hexanes to 20% Et₂O/hexanes to yield the title compound (0.89 g, 3.89 mmol) as a white solid. ^1H NMR (CDCl_3 , 300 MHz) δ 9.87 (s, 1H), 7.70 (d, 1H), 7.20 (d, 1H), 7.15 (d, 1H), 6.91 (d, 1H).

30 B. 5'-Chloro-[2,2']bithiophenyl-5-carboxylic acid.

The title compound is prepared as described in EXAMPLE 28, Part B using 5'-chloro-[2,2']bithiophenyl-5-carbaldehyde. ^1H NMR (CDCl_3 , 300 MHz) δ 7.69 (d, 1H), 7.09 (d, 1H), 7.06 (d, 1H), 6.89 (d, 1H). EI MS, $[\text{M}]^+=243,245$ (Cl pattern).

35 EXAMPLE 33. 7-Chloro-isoquinoline-3-carboxylic acid.

A. 7-Chloro-isoquinoline-3-carbaldehyde.

A 20mL of 80% H_2SO_4 is added 7-chloro-3,3-dibromomethyl isoquinoline (0.69g, 2.06mmol) is heated to 150°C for 16 hours. The solution is then cooled to ambient temperatures and diluted with 40 mL of H_2O . The resulting solution is basified to pH=11 with 1N NaOH. The aqueous solution is extracted with CH_2Cl_2 . The organic solution is washed with H_2O and a saturated NaCl solution. The organic layer is dried over $MgSO_4$, filtered and concentrated to give the product as an oil (0.25g, 1.3 mmol). 1H NMR ($CDCl_3$, 300MHz) δ 10.0 (s, 1H), 9.30 (s, 1H), 8.36 (s, 1H), 8.07 (s, 1H), 7.95 (d, 1H), 7.78 (d, 1H). MS (EI): m/z 191, 193 (M+), Cl pattern.

10 B. 7-Chloro-isoquinoline-3-carboxylic acid.

To 4.5 mL of a 1N NaOH solution at 0°C is added a solution of $AgNO_3$ (0.31g, 1.8mmol) in 3 mL of H_2O , followed by a solution of 7-chloro-isoquinoline-3-carbaldehyde (0.25g, 1.3mmol) in 3 mL of EtOH. The solution is stirred at 0°C for 10 minutes, then at room temp. For 3 hours. The solution is acidified to pH=3 with 1H HCl. The resulting solution is extracted with $CHCl_3$. The organic layer is dried over $MgSO_4$, filtered and concentrated to give the product as a white solid (0.2g, 0.96mmol). 1H NMR (CD_3OD , 300MHz) δ 9.18 (s, 1H), 8.63 (s, 1H), 8.18 (m, 1H), 7.80 (m, 2H), 6.94 (m, 1H), 4.15 (q, 2H), 3.48 (s, 2H), 1.20 (t, 3H). MS (EI): m/z 208, 210 (M+), Cl pattern.

20 EXAMPLE 34. 2-Acetylamino-3-(5-chloro-thiophen-2-yl)-acrylic acid.A. 4-(5-Chloro-thiophen-2-ylmethylene)-2-methyl-4H-oxazol-5-one.

A mixture consisting of 5-chlorothiophene-2-carboxaldehyde (1.00 g, 6.82 mmol), N-acetylglycine (0.96 g, 8.18 mmol), NaOAc (0.67 g, 8.18 mmol) in Ac_2O (5 mL) is warmed at reflux for 16 hours. The reaction mixture is cooled to ambient temperature and diluted with dilute aqueous NaOH (0.5 M, 100 mL) and CH_2Cl_2 (100 mL). The layers are separated and the organic phase is washed with aqueous $NaHCO_3$, brine, dried over anhydrous Na_2SO_4 , filtered and concentrated to provide 1.5 g (100%) of the title compound as a colorless oil which is used without further purification in the next reaction. 1H NMR (300 MHz, $CDCl_3$) δ 2.39 (s, 3H), 6.94 (d, J = 4.0 Hz, 1H), 7.21 (s, 1H), 7.26 (d, J = 4.0 Hz, 1H) ppm.

30 B. 2-Acetylamino-3-(5-chloro-thiophen-2-yl)-acrylic acid.

To a solution containing 4-(5-chloro-thiophen-2-ylmethylene)-2-methyl-4H-oxazol-5-one (1.5 g, 6.82 mmol) in MeOH (18 mL) is added 1.0 M NaOH (12.0 mL, 12 mmol) at ambient temperature. After 3 h, the reaction mixture is diluted with water (100 mL) and CH_2Cl_2 (100 mL) and the layers are separated. The basic, aqueous layer is washed with CH_2Cl_2 and then acidified using 1.0 M HCl (20 mL) to provide a crude solid which is collected on a Buchner

funnel. Drying in vacuo provided 1.2 g (75%) of the title compound as a pale brown solid which is used without further purification. ^1H NMR (300 MHz, DMSO- d_6) δ 2.00 (s, 3H), 7.14 (d, J = 4.01 Hz, 1H), 7.38 (d, J = 4.01 Hz, 1H), 7.63 (s, 1H), 9.28 (s, 1H), 12.73 (br s, 1H) ppm; MS (EI): m/z 245 (M $^+$).

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EXAMPLE 35. 2-Acetylamino-3-(5-chloro-thiophen-2-yl)-propionic acid.

To a solution containing 2-acetylamino-3-(5-chloro-thiophen-2-yl)-acrylic acid (1.00 g, 4.08 mmol) and K_2CO_3 (1.70 g, 12.1 mmol) in DMF (20 mL) is added MeI (0.87 g, 6.12 mmol) at ambient temperature. After 2 h, the reaction mixture is diluted with water (100 mL) and EtOAc (100 mL) and the layers are separated. The aqueous layer is extracted with EtOAc (50 mL) and the combined organic phase is washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated to provide 0.92 g (83%) of the methyl ester which is used without further purification. ^1H NMR (300 MHz, CDCl_3) δ 2.19 (s, 3H), 3.77 (s, 3H), 6.86 (d, J = 4.02 Hz, 1H), 6.99 (m, 1H), 7.05 (d, J = 4.02 Hz, 1H), 7.64 (s, 1H) ppm.

15 A small Parrot vessel is charged with the crude ester (0.85 g, 3.13 mmol) and $(\text{Ph}_3\text{P})_3\text{RhCl}$ (0.10 g, 0.10 mmol) in MeOH (50 mL). The vessel is pressurized to 50 PSI H_2 pressure and agitated for 7 h at ambient temperature. The reaction mixture is then filtered and concentrated to provide the desired compound, which is used without further purification. MS (EI): m/z 261 (M $^+$).

20 The above-prepared saturated ester is dissolved in a 1:1:1 solution of water/THF/MeOH (15 mL). LiOH monohydrate (0.14 g, 3.23 mmol) is added and the heterogeneous mixture is stirred for 16 hours. The reaction mixture is diluted with water (100 mL) and EtOAc (100 mL) and the layers are separated. The aqueous layer is extracted with EtOAc (50 mL) and the combined organic phase is washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated to provide 0.62 g (81%) of the title compound as a colorless oil. ^1H NMR (300 MHz, CDCl_3) δ 2.02 (s, 3H), 3.30 (m, 2H), 4.81 (m, 1H), 6.45 (br d, J = 6.45 Hz, 1H), 6.58 (d, J = 3.68 Hz, 1H), 6.71 (d, J = 3.68 Hz, 1H), 9.79 (br s, 1H) ppm; MS (EI): m/z 247 (M $^+$).

EXAMPLE 36. 3-(6-Amino-pyridin-3-yl)-acrylic acid.

30 A. N-(5-Bromo-pyridin-2-yl)-acetamide.

Triethylamine (17.7 mL, 75 mmol) is added to a mixture of 2-amino-5-bromopyridine (5.0 g, 29 mmol) and acetic acid (7.1 mL, 75 mmol). The solution is heated to reflux for 48 hours. After this time, the solution is concentrated. The residue is dissolved in water and the pH is adjusted to 10 with 1N NaOH. The solids are collected by filtration. The crude product is

recrystallized from boiling water to give the title compound (2.6 g 12.0 mmol) as a white solid.

¹H NMR (300 MHz, CDCl₃) δ 10.62 (1H, bs), 8.42 (s, 1H), 8.01 (m, 2H), 2.05 (s, 3H).

B. 3-(6-Acetylamino-pyridin-3-yl)-acrylic acid

To a mixture of N-(5-bromo-pyridin-2-yl)-acetamide (1.26 g, 5.86 mmol) and tri-n-

5 butylamine in xylenes (10 mL) is added Pd(OAc)₂ (1.4 mg, 0.006 mmol) and triphenyl phosphine (15.4mg, 0.06 mmol). Acrylic acid (0.48 mL, 7.03 mmol) is then added dropwise over 5 minutes. The mixture is heated to reflux for 5 hours. The solution is cooled to ambient temperatures. The mixture is diluted with water and the pH is adjusted to 4 with 1N HCl. The solution is extracted with EtOAc/CH₂Cl₂ (2:1). The resulting suspension is filtered to give the title

10 compound (0.80 g, 3.88 mmol) as a white solid. MS (ion spray) 207, (M+H).

C. 3-(6-Amino-pyridin-3-yl)-acrylic acid

To 3-(6-acetylamino-pyridin-3-yl)-acrylic acid (0.80 g, 3.88 mmol) in ethanol (10 mL) is

added 1N NaOH (20mL). The solution is heated to reflux. After 16 h, the solution is

concentrated to 1/3 its volume. The aqueous solution is diluted with water and acidified to

15 pH=2 with 6N HCl. The solution is concentrated to dryness. The residue is dissolved in

methanol. The solution is filtered. The organic solution is concentrated. The crude product is

purified by RP-HPLC eluting with a gradient of 5%CH₃CN/H₂O (0.1% TFA) to 30%

CH₃CN/H₂O (0.1%TFA) to give the product as a white solid (0.54 g, 1.93 mmol). ¹H NMR (300

MHz, CD₃OD) δ 8.34 (d, 1H), 8.07 (s, 1H), 7.54 (d, 2H), 7.06 (d, 1H), 6.47 (d, 1H). MS (ion

20 spray) 165, (M+H).

EXAMPLE 37. 4-Chloro-benzyl isocyanate.

To a solution of triphosgene (0.54 g, 1.85 mmol) in 10 mL of dry CH₂Cl₂ at 0°C is added

4-chloro-benzylamine (0.61 mL, 5.00 mmol) dropwise as a white precipitate forms. Et₃N (1.39

25 mL, 10.0 mmol) in 5 mL of CH₂Cl₂ is added immediately and the resulting mixture is stirred at

0°C for 5 min, then at room temperature for 3 hours. The mixture is concentrated in vacuo and

triturated with EtOAc. The white precipitate (triethylamine hydrochloride) is filtered off and the

filtrate is concentrated. The title compound (6.20 g, 30.6 mmol) is isolated as a crude yellow

residue and used in the subsequent step without further purification. ¹H NMR (CDCl₃, 300

30 MHz) δ 7.35 (d, 2H), 7.25 (d, 2H), 4.50 (s, 2H).

EXAMPLE 38. 5-Chloro-thiophene-2-carbonyl azide.

To a solution of 5-chloro-2-thiophene-carboxylic acid (5.00 g, 30.7 mmol) in 130 mL of

acetone is added Et₃N (4.29 mL, 30.7 mmol). The mixture is cooled to 0°C and ethyl

35 chloroformate (3.23 mL, 33.8 mmol) is added. The mixture is stirred at 0°C for 1h and sodium

azide (3.40 g, 52.3 mmol) is added. The mixture is stirred at 0°C for 2 h, then poured into 300 mL of ice water and the aqueous layer is extracted with CH_2Cl_2 (2x). The combined organics are washed with water (2x) and brine, then dried, filtered and concentrated. The crude residue is purified via flash column chromatography eluting with 10% EtOAc/hexanes to provide the title 5 compound (3.00 g, 16.0 mmol) as a white solid. ^1H NMR (CDCl_3 , 300 MHz) δ 7.67 (d, 1H), 6.99 (d, 1H).

EXAMPLE 39. 4-Nitro-2,3,5,6-tetrachloropyridine.

Pentachloropyridine (80 g, 320 mmol) is treated with benzyl amine (104 mL, 96 mmol), 10 dissolved in dioxane (1 L) and refluxed for 16 hours. The reaction mixture is cooled to ambient temperature and the precipitated white solid is removed by filtration. The filtrate is concentrated to a brown residue and triturated with 4 % ethyl acetate in hexane (3 X 250 mL) to give 4-benzylamino-2,3,5,6-tetrachloropyridine as an off-white solid (40 g, 124 mmol). This material is dissolved in chloroform (400 mL), cooled in an ice bath and treated with trifluoroacetic acid (500 15 mL) and 30% hydrogen peroxide (100 mL). The reaction mixture is warmed to room temperature overnight and treated with additional trifluoroacetic acid (500 mL) and 30% hydrogen peroxide (100 mL). After stirring 24 hours the reaction is treated with water (1L). The lower organic layer is separated and the aqueous layer is extracted with chloroform. The combined organic layers are concentrated to a solid residue and redissolved in ethyl 20 acetate/hexane (30 mL). The suspended orange solid is removed and the filtrate is loaded on a silica flash column. The column is eluted with hexane and the title compound is collected as a white solid (15.6 g, 60 mmol). EI MS m/z 260, 262, 264 [M+].

EXAMPLE 40. 4-(tert-Butyloxycarbonyl)-piperazin-2-one

25 4-(Benzylloxycarbonyl)-piperazin-2-one (2.2 g, 9.4 mmol) and Boc anhydride (2.5 g, 11.3 mmol) are dissolved in methanol (100 mL), treated with 5% Pd /C and shaken 16 h under hydrogen gas (30 PSI). The reaction vessel contents are filtered through Celite and the filtrate is concentrated to yield 4-(tert-Butyloxycarbonyl)-2-oxopiperazine (1.9 g, 9.4 mmol) which is used without further purification. EI MS m/z 200, M⁺; ^1H NMR (CDCl_3 , 300 MHz) δ 6.17 (br, 1H), 4.20 (s, 2H), 3.55 (t, 2H), 3.38 (m, 2H), 1.48 (s, 9H).

EXAMPLE 41. 2-Methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

A. N-Cbz-O-methylserine-aminoacetaldehyde dimethyl acetal.

To a solution of N-Cbz-O-methylserine (10.8g, 41.8mmol) in 500mL of CH_2Cl_2 is added 35 Et_3N (12.7 g, 125mmol). The solution is cooled to 0°C and TBTU (13.5g, 42mmol) and

aminoacetaldehyde dimethyl acetal (4.83g, 46mmol) are added. The solution is stirred for 16 hours. The solution is diluted with 500mL of ether. The resulting solution is washed with water, 1N KHSO₄, and sat. NaCl. The title compound (13.7g, 41.8mmol) is obtained as a white foam.

¹H NMR (CDCl₃, 300MHz) δ 7.40 (m, 5H), 6.55 (bs, 1H), 5.66 (bs, 1H), 5.32 (m, 1H), 5.13 (s, 5) 2H), 4.32 (m, 2H), 3.79 (dd, 1H), 3.44 (m, 2H), 3.40 (m, 9H).

B. N-Cbz-2-Oxo-3-(S)-methoxymethyl-(4,5-dihydro)piperazine.

To a solution of N-Cbz-O-methylserine-aminoacetaldehyde dimethyl acetal (13.7g, 41.8mmol) in 300mL of toluene is added TsOH.H₂O (0.80g, 4.2mmol). The solution is heated to 60°C. After 5h, the solution is diluted with ether. The resulting organic solution is washed with water, sat. NaHCO₃, and sat. NaCl. The organic layer is dried over MgSO₄, filtered and concentrated under vacuum. The resulting crude product is purified by column chromatography eluting with a gradient of 10%EtOAc:CH₂Cl₂ to 20%EtOAc:CH₂Cl₂. The title compound (10.7g, 38mmol) is obtained as a white solid. ¹H NMR (CDCl₃, 300MHz) δ 7.36 (m, 5H), 6.45 and 6.30 (d, 1H rotational isomers), 5.61 and 5.50 (d, 1H rotational isomers), 5.20 (s, 2H), 4.92 and 4.83 (bs, 1H rotational isomers), 3.63 (m, 3H), 3.32 and 3.20 (s, 1H rotational isomers).

C. 2-Methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

To a solution of N-Cbz-2-oxo-3-(S)-methoxymethyl-(4,5-dihydro)piperidine (10.7g, 38mmol) in 50mL of methanol is added Pt/C (1gm, 10% by weight). The atmosphere above the reaction is replaced by hydrogen. After 24h, the solution is filtered and the filtrate is washed with methanol. The collected organic solutions are concentrated under vacuum. The resulting crude product is purified by column chromatography eluting with a gradient of 2%MeOH/CH₂Cl₂ to 5%MeOH/CH₂Cl₂. The title compound (6.0g, 22mmol) is obtained as a white solid. ¹H NMR (CDCl₃, 300MHz) δ 7.35 (m, 5H), 6.42 (bs, 1H), 5.20 (AB, 2H), 4.58 (m, 1H), 4.18 (m, 1H), 3.95 (m, 1H), 3.50 (m, 4H), 3.27 (s, 3H).

25

EXAMPLE 42. 2-Butyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

The title compound is prepared as in EXAMPLE 41, substituting Cbz-norleucine for Cbz-O-methyl-serine. ¹H NMR (CDCl₃, 300MHz) δ 7.32 (m, 5H), 5.13 (AB, 2H), 4.60 (m, 1H), 4.13 (m, 1H), 3.38 (m, 2H), 3.23 (m, 2H), 1.90 (m, 1H), 1.66 (m, 1H), 1.29 (m, 4H), 0.89 (m, 3H). MS (ion spray) m/z 291, (M+H).

EXAMPLE 43. 2-Ethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

The title compound is prepared as in EXAMPLE 41, substituting Cbz-2-amino-butric acid for Cbz-O-methyl-serine. ¹H NMR (CDCl₃, 300MHz) δ 7.37 (m, 5H), 6.55 (bs, 1H), 5.10 (AB,

2H), 4.57 (m, 1H), 4.24 (m, 1H), 3.42 (m, 1H), 3.26 (m, 2H), 2.20 (m, 1H), 1.81 (m, 1H), 0.96 (m, 3H).

EXAMPLE 44. 2-Propyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

The title compound is prepared as in EXAMPLE 41, substituting Cbz-norvaline for Cbz-O-methyl-serine. ^1H NMR (CDCl_3 , 300MHz) δ 7.32 (m, 5H), 7.00 (bs, 1H), 5.12 (AB, 2H), 4.58 (m, 1H), 4.21 (m, 1H), 3.40 (m, 1H), 3.19 (m, 2H), 1.88 (m, 1H), 1.73 (m, 1H), 1.37 (m, 2H), 0.91 (m, 3H). MS (ion spray) m/z 277, (M+H).

EXAMPLE 45. 2-Ethoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

The title compound is prepared as in EXAMPLE 41, substituting Cbz-O-ethyl-serine for Cbz-O-methyl-serine. ^1H NMR (CDCl_3 , 300MHz) δ 7.32 (m, 5H), 6.96 (bs, 1H), 5.17 (AB, 2H), 4.58 (m, 1H), 4.18 (m, 1H), 4.03 (m, 1H), 3.66 (m, 2H), 3.44 (m, 3H), 3.27 (s, 1H), 1.06 (m, 3H). MS (ion spray) m/z 293, (M+H).

EXAMPLE 46. 2-Methyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

The title compound is prepared as in EXAMPLE 41, substituting Cbz-alanine for Cbz-O-methyl-serine. ^1H NMR (CDCl_3 , 300MHz) δ 7.34 (m, 5H), 7.02 (bs, 1H), 5.17 (AB, 2H), 4.65 (m, 1H), 4.17 (m, 1H), 3.42 (m, 1H), 3.23 (m, 2H), 1.41 (d, 3H). MS (EI) m/z 248, (M+).

EXAMPLE 47. 2-Benzyl-3-oxo-piperazine-1-carboxylic acid benzyl ester

The title compound is prepared as in EXAMPLE 41, substituting Cbz-phenylalanine for Cbz-O-methyl-serine. ^1H NMR (CDCl_3 , 300MHz) δ 7.22 (m, 10H), 7.00 (bs, 1H), 5.10 (AB, 2H), 4.10 (m, 1H), 3.27 (m, 2H), 3.10 (m, 2H), 2.55 (m, 2H). MS (EI) m/z 324, (M+).

EXAMPLE 48. 2-(1-Methoxyethyl)-3-oxo-piperazine-1-carboxylic acid benzyl ester.

The title compound is prepared as in EXAMPLE 41, substituting Cbz-O-methyl-threonine for Cbz-O-methyl-serine. ^1H NMR (CDCl_3 , 300MHz) δ 7.52 (bs, 1H), 7.22 (m, 5H), 5.12 (AB, 2H), 4.33 (m, 1H), 4.05 (m, 2H), 3.60 (m, 1H), 3.14 (s, 3H), 3.10 (m, 1H), 2.82 (m, 1H), 1.10 (d, 3H). MS (ion spray) m/z 293, (M+H).

30

EXAMPLE 49. 2,2-Dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

The title compound is prepared as in EXAMPLE 41, substituting Cbz-2-amino-isobutyric acid for Cbz-O-methyl-serine. ^1H NMR (CDCl_3 , 300MHz) δ 7.36 (m, 5H), 6.52 (bs, 1H), 5.12 (s, 2H), 3.72 (m, 2H), 3.33 (m, 2H), 1.68 (s, 3H), 1.64 (s, 3H). MS (EI) m/z 262, (M+).

35

EXAMPLE 50. 2-Isopropyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

The title compound is prepared as in EXAMPLE 41, substituting Cbz-valine for Cbz-O-methyl-serine. ^1H NMR (CDCl₃, 300MHz) δ 7.36 (m, 5H), 5.88 (bs, 1H), 5.10 (s, 2H), 4.35 (m, 1H), 3.44 (m, 1H), 3.27 (m, 2H), 2.31 (m, 1H), 1.00 (d, 3H), 0.94 (d, 2H).

5

EXAMPLE 51. 2-Isobutyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

The title compound is prepared as in EXAMPLE 41, substituting Cbz-leucine for Cbz-O-methyl-serine. ^1H NMR (CDCl₃, 300MHz) δ 7.35 (m, 5H), 6.50 (m, 1H), 5.15 (s, @H), 4.18 (m, 1H), 3.42 (m, 2H), 3.21 (m, 2H), 1.50 (m, 3H), 0.90 (m, 6H).

10

EXAMPLE 52. 2-(2-Methoxyethyl)-3-oxo-piperazine-1-carboxylic acid benzyl ester.

The title compound is prepared as in EXAMPLE 41, substituting Cbz-O-methyl-homo-serine for Cbz-O-methyl-serine. ^1H NMR (CDCl₃, 300MHz) δ 7.32 (m, 5H), 6.85 (bs, 1H), 5.14 (s, 2H), 4.75 (m, 2H), 4.20 (m, 2H), 3.42 (m, 1H), 3.21 (m, 3H), 2.12 (m, 4H).

15

EXAMPLE 53. 2-Methoxymethyl-5-methyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

The title compound is prepared as in EXAMPLE 41, substituting 2-amino-propionaldehyde dimethyl acetal for aminoacetaldehyde dimethyl acetal. ^1H NMR (CDCl₃, 300MHz) δ 7.42 (m, 5H), 6.96 (bs, 1H), 5.12 (AB, 2H), 4.52 (m, 1H), 4.21 (m, 1H), 3.92 (m, 1H), 3.58 (m, 2H), 3.22 (s, 3H), 3.10 (m, 1H), 0.95 (m, 3H).

20

EXAMPLE 54. 3-(R)-(tert-Butyl-dimethyl-silyloxy)methyl)-5-oxo-piperazine-1-carboxylic acid benzyl ester.A. 2-tert-Butoxycarbonylamino-3-(tert-butyl-dimethyl-silyloxy)-propionic acid.

25 tert-Butyldimethylchlorosilane (32.3 g, 0.214 mol) in THF (50 mL) is added dropwise via cannula to a solution of BOC serine (20.0g, 0.098 mol) and imidazole (15.3 g, 0.224 mol) in THF (360 mL) at RT. The resulting slurry is stirred for 2.5 h then the solvent is removed in vacuo. The crude product is dissolved in MeOH (180 mL) and 5N NaOH (58 mL) is slowly added at RT. The mixture is stirred for 3 h then diluted with water (180 mL) after which time the aqueous layer is washed with ether (180 mLx2). The aqueous layer is acidified to pH 4-5 with 2N HCl and extracted with diethyl ether. The organic layer is washed with saturated NaHCO₃ and brine then dried over MgSO₄, filtered and concentrated to dryness. The crude product (12.67g, 0.040 mol) is used in the subsequent step without further purification. ^1H NMR (CDCl₃, 300 MHz) δ 5.35 (bs, 1H), 4.30 (bs, 1H), 4.13 (dd, 1H), 3.80 (dd, 1H), 1.45 (s, 9H), 0.98 (s, 9H), 0.10 (s, 6H). EI MS, [M+H]⁺=320.

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B. [2-(tert-Butyl-dimethyl-silyloxy)-1-(methoxy-methyl-carbamoyl)-ethyl]-carbamic acid tert-butyl ester.

N,N-Dimethylaminopyridine (2.60 g, 21.3 mmol) and BOP reagent (18.15 g, 41.0 mmol) are added to a solution of 2-tert-butoxycarbonylamino-3-(tert-butyl-dimethyl-silyloxy)-
5 propionic acid (12.37 g, 38.7 mmol), diisopropylethylamine (8.1 mL, 46.4 mmol) and N,O-dimethylhydroxylamine hydrochloride (4.53 g, 46.4 mmol) in THF (260 mL) at RT. The resulting suspension is stirred at RT overnight then concentrated to dryness. The residue is diluted with EtOAc and washed with saturated NH₄Cl, saturated NaHCO₃ and brine. The organic layer is dried over MgSO₄, filtered and concentrated in vacuo to give the crude product which is purified
10 by flash chromatography eluting with 10-30% EtOAc/Hexanes to yield the title compound (11.86 g, 30.37 mmol) as an oil. ¹H NMR (CDCl₃, 300 MHz) δ 5.35 (bd, 1H), 4.71 (bs, 1H), 3.78-3.85 (m, 2H), 3.72 (s, 3H), 3.20 (s, 3H), 1.42 (s, 9H), 0.90 (s, 9H), 0.05 (s, 6H).

C. [1-(tert-Butyl-dimethyl-silyloxy)methyl]-2-oxo-ethyl]-carbamic acid tert-butyl ester.

A solution of [2-(tert-butyl-dimethyl-silyloxy)-1-(methoxy-methyl-carbamoyl)-ethyl]-
15 carbamic acid tert-butyl ester (11.86, 30.37 mmol) in Et₂O (100 mL) is added dropwise to a 1.0M solution of LAH in ether (35.5 mL) at -5°C-0°C. The resulting mixture is stirred for 2.5 h then an aqueous solution of KHSO₄ is slowly added. The reaction mixture is stirred for 30 minutes and then washed with saturated NH₄Cl, saturated NaHCO₃ and brine. The organic layer is dried over MgSO₄, filtered and concentrated in vacuo to give the crude product which is purified
20 by flash chromatography eluting with 30% EtOAc/Hexanes to yield the title compound (6.04 g, 19.9 mmol) as an oil. ¹H NMR (CDCl₃, 300 MHz) δ 9.65 (s, 1H), 5.30 (bs, 1H), 4.20 (m, 1H), 3.65 (4.90 (m, 2H), 1.48 (s, 9H), 0.90 (s, 9H), 0.05 (s, 6H). Ion spray MS, [M+H]⁺=304.

D. [2-tert-Butoxycarbonylamino-3-(tert-butyl-dimethyl-silyloxy)-propylamino]-acetic acid methyl ester.

25 Sodium cyanoborohydride (2.63 g, 41.9 mmol) is added to a solution of [1-(tert-butyl-dimethyl-silyloxy)methyl]-2-oxo-ethyl]-carbamic acid tert-butyl ester (6.04 g, 19.9 mmol) and glycine methyl ester hydrochloride (2.75 g, 32.9 mmol) in MeOH (500 mL). The mixture is stirred for 2 days at RT then concentrated to dryness. The crude product is purified by flash chromatography eluting with 1-5% MeOH/CH₂Cl₂ to yield the title compound (3.06, 8.12 mmol)
30 as a colorless oil. ¹H NMR (CDCl₃, 300 MHz) δ 5.00 (bs, 1H), 3.75 (s, 3H), 3.60-3.70 (m, 4H), 3.40 (d, 1H), 2.80 (dd, 1H), 2.68 (dd, 1H), 1.40 (s, 9H), 0.90 (s, 9H), 0.05 (s, 6H). Ion spray MS, [M+H]⁺=377.

E. (Benzylloxycarbonyl-[2-tert-butoxycarbonylamino-3-(tert-butyl-dimethyl-silyloxy)-propyl]-amino)-acetic acid methyl ester.

Benzylchloroformate (1.4 mL, 9.81 mmol) is added dropwise to a solution of N,N-dimethylaminopyridine (1.09 g, 8.93 mmol) and [2-tert-butoxycarbonylamino-3-(tert-butyl-dimethyl-silyloxy)-propylamino]-acetic acid methyl ester (3.06 g, 8.12 mmol) in CH_2Cl_2 at RT. The resulting mixture is stirred overnight then concentrated to dryness. The crude product is 5 purified by flash chromatography eluting with 1% MeOH/ CH_2Cl_2 to yield the title compound (3.52 g, 6.89 mmol) as a colorless oil. Ion spray MS, $[\text{M}+\text{H}]^+=511$.

F. 3-(tert-Butyl-dimethyl-silyloxy)methyl)-5-oxo-piperazine-1-carboxylic acid benzyl ester
(Benzoyloxycarbonyl-[2-tert-butoxycarbonylamino-3-(tert-butyl-dimethyl-silyloxy)-propyl]-amino)-acetic acid methyl ester (3.52 g, 6.89 mmol) is stirred in 50% TFA/ CH_2Cl_2 (40 mL) at RT for 40 minutes. The reaction mixture is concentrated in vacuo and the crude product is 10 purified by flash chromatography eluting with 1% MeOH/ CH_2Cl_2 to yield the title compound (1.1 g, 2.9 mmol) as a colorless oil. Ion spray MS, $[\text{M}+\text{H}]^+=379$.

EXAMPLE 55. 5-Oxo-piperazine-1,3(R or S)-dicarboxylic acid 1-benzyl ester 3-methyl ester.
15 N,N-Dimethylaminopyridine (0.43 g, 3.5 mmol) and benzylchloroformate (0.55 g, 3.8 mmol) are added to a solution of methyl 6-oxopiperazine-2-carboxylate (0.50 g, 3.2 mmol) (Aebischer, B., *Helv. Chim. Acta* 1989, 72, 1043-1051) in CH_2Cl_2 at RT. After 1 h, the reaction mixture is poured into EtOAc and washed with saturated NaHCO_3 and brine then dried over MgSO_4 , filtered and concentrated to dryness to give a solid (0.90 g, 3.1 mmol) which is used in 20 subsequent reactions without further purification. ^1H NMR (CDCl_3 , 300 MHz) δ 7.40 (bs, 5 H), 6.32 (bs, 1H), 5.15 (s, 2H), 4.00-4.30 (m, 3H), 4.23 (s, 3H), 3.70-3.80 (m, 2H). MS (EI) m/z 292 (M^+).

EXAMPLE 56. (S)-5-Oxo-piperazine-1,3-dicarboxylic acid 1-allyl ester 3-methyl ester.
25 To a solution containing methyl (S)-6-oxopiperazine-2-carboxylate (1.32 g, 8.35 mmol), prepared by the method of Aebischer, in anhydrous dichloromethane (30 mL) at 0 °C is added triethylamine (1.26 g, 12.5 mmol) followed by allylchloroformate (1.20 g, 10.0 mmol). After 1 h, the reaction mixture is poured onto a 1:1 mixture of CH_2Cl_2 /water (200 mL), acidified using 1 N HCl and the layers are separated. The organic phase is washed with brine, dried over 30 anhydrous Na_2SO_4 , filtered and concentrated. The crude residue is chromatographed on silica gel (CH_2Cl_2 to 1% MeOH/ CH_2Cl_2) to provide 1.22 g (60%) of EXAMPLE 35 as a viscous oil. ^1H NMR (300 MHz, CDCl_3) δ 6.43 (bs, 1H), 5.90 (m, 1H), 5.26 (m, 2H), 4.61 (m, 2H), 4.05-4.26 (m, 3H), 3.80 (s, 3H), 3.72 (m, 2H); MS (ISP loop): m/z 243 (M^+).

35 EXAMPLE 57. (2S, 6R)-4-(2,6-dimethyl)-3-oxo-piperazine-1-carboxylic acid benzyl ester and

EXAMPLE 58. (2S, 6S)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.A. (2RS, 1S)-[1-(2-hydroxy-propylcarbamyl)-ethyl]-carbamic acid tert-butyl ester

N-(tert-Butoxycarbonyl)-L-alanine (10.0 g, 52.8 mmol) is dissolved in 150 mL of THF.

Once the triethylamine (11.0 ml, 79.2 mmol) is added, the solution is cooled to 0°C. Isopropyl 5 chloroformate in toluene (1M) (52.8 ml, 52.8 mmol) is added slowly followed by the addition of (2RS) 1-amino-2-propanol (6.1 ml, 79.2 mmol). After stirring overnight, the mixture is washed with 1N sodium hydroxide and 1N hydrochloric acid. Concentration of the organic solvent afforded (2RS, 1S)-[1-(2-hydroxy-propylcarbamyl)-ethyl]-carbamic acid tert-butyl ester (9.92 g, 76% yield) as a clear oil.

B. (1S)-[1-(2-oxo-propylcarbamoyl)-ethyl]-carbamic acid tertbutyl ester

Dimethylsulfoxide (7.16 ml, 100.8 mmol) is added to a solution of oxalyl chloride (4.41 ml, 50.4 mmol) in 126 mL of methylene chloride at -78 °C. The mixture is left to stir for fifteen minutes, and a solution of (2RS, 1S)-[1-(2-hydroxy-propylcarbamyl)-ethyl]-carbamic acid tert-butyl ester (9.92 g, 40.32 mmol) in 100 mL of CH_2Cl_2 is added dropwise. After stirring for 15 minutes at -15 78 °C, the reaction is quenched with triethylamine (28 mL, 381 mmol), and the temperature is allowed to rise to room temperature. The volatile solvents are removed, and the residue is purified by flash column (SiO_2 , 60% EtOAc/Hexane). The product (1S)-[1-(2-oxo-propylcarbamoyl)-ethyl]-carbamic acid tertbutyl ester (5.93 g, 60 %) is isolated as a white solid.

MS $\text{C}_{11}\text{H}_{20}\text{N}_2\text{O}_4$ MS m/z: 245.

C: (3S, 5RS)-3,5-dimethyl-piperazin-2-one.

(1S)-[1-(2-oxo-propylcarbamoyl)-ethyl]-carbamic acid tertbutyl ester (5.93 g, 24.3 mmol) is stirred in a solution of 30 % trifluoroacetic acid in methylene chloride (100 mL) for three hours. The solvents are removed in vacuo. The residue is dissolved in 50 mL of MeOH and transferred to a par bottle. Palladium on carbon (10 %, 1.0 g) is added, and the mixture is 25 hydrogenated under pressure for 24 hours. The catalyst is filtered off; the MeOH is removed in vacuo to afford (3S, 5RS)-3,5-dimethyl-piperazin-2-one which is directly protected with a benzyl carbamate without further purification.

D: (2S, 6RS)-2,6-Dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

To a solution of (3S, 5RS)-3,5-dimethyl-piperazin-2-one (24.3 mmol) in 100 mL of 30 methylenechloride is added triethylamine (8.45 mL, 60.75 mmol) and N-(benzyloxycarbonyloxy)succinimide (12.1 g, 48.6 mmol). After stirring overnight, the CH_2Cl_2 is removed, and the crude mixture is chromatographed (50 % EtOAc/Hexane). (2S, 6RS)-2,6-Dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (3.3 g, 52 % yield over three steps) is isolated as a white powder. MS $\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}_3$ MS m/z: 263.

E. (2S, 6R)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester and (2S, 6S)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester

The two single enantiomers [(2S, 6R)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester and (2S, 6S)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester] can be separated by column chromatography from (2S, 6RS)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester, which can also be used directly in combination or separation of its derivatives as shown below.

EXAMPLE 59. (2S, 6R)-4-(2,4-Dimethoxy-benzyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

A. (2S, 2S)-N-(2, 4-dimethoxy-benzyl)-N-(2-hydroxy-propyl)-2-(2,2,2-trifluoroacetylamino)-propionamide.

To a slurry of (2S)-2-(2,2,2-trifluoroacetylamino)-propionic acid (15.3 g, 53.4 mmol) in 120 mL of methylene chloride is added triethylamine (5.6 mL, 40.0 mmol). The heterogeneous mixture is cooled to 0°C and isopropyl chloroformate (27 mL, 27.0 mmol) is added slowly. After stirring for 20 minutes at room temperature, a solution of the (2S)-1-(2,4-dimethoxybenzylamino)-propan-2-ol (6.0 g, 26.7 mmol, obtained from the reductive amination of the corresponding aldehyde and aminoalcohol) in 5mL of methylene chloride is added. The resulting mixture is left to stir overnight. Ethyl acetate (500 mL) is added, and the organic solution is washed with 1N hydrochloric acid (50 mL) and 1N sodium hydroxide (50 mL). The ethyl acetate is dried with magnesium sulfate, filtered and condensed. The resulting residue is chromatographed on silica gel (25% ethyl acetate/hexane) to give (2S, 2S)-N-(2,4-dimethoxybenzyl)-N-(2-hydroxy-propyl)-2-(2,2,2-trifluoroacetylamino)-propionamide (6.29g, 60% yield) as a clear oil. MS C₁₇H₂₃F₃N₂O₅ MS m/z: 393.

B. (3S, 5R)-1-(2,4-dimethoxy-benzyl)-3,5-dimethyl-4-trifluoroacetyl-piperazin-2-one.

(2S, 2S)-N-(2,4-Dimethoxy-benzyl)-N-(2-hydroxypropyl)-2-(2,2,2-trifluoroacetylamino)-propionamide (3.64 g, 9.29 mmol) is dissolved in 25 mL of tetrahydrofuran. Triphenylphosphate (3.65 g, 14.0 mmol) is added, and the resulting mixture is cooled to 0 °C before diethyl azodicarboxylate (2.2 mL, 14 mmol) is added slowly. The resulting mixture is left to stir overnight. The reaction mixture is condensed, and the residue is purified by column chromatography (SiO₂, 25% ethyl acetate/hexane). The desired product, (3S, 5R)-1-(2,4-dimethoxy-benzyl)-3,5-dimethyl-4-trifluoroacetyl-piperazin-2-one (1.5 g, 43% yield), is isolated as a clear oil.

C. (3S, 5R)-1-(2,4-Dimethoxy-benzyl)-3,5-dimethyl-piperazin-2-one.

(3S, 5R)-1-(2,4-Dimethoxy-benzyl)-3,5-dimethyl-4-trifluoroacetyl-piperazin-2-one (575 mg, 1.54 mmol) is dissolved in 30 mL of methanol and 3 mL of H₂O. Potassium carbonate (883 mg, 6.4 mmol) is added to the solution, and the reaction is refluxed for one and half hours before concentration. Ethyl acetate (3x 50 mL) is used to extract the aqueous layer. Removal of 5 Ethyl acetate afforded the crude amine (387 mg, 91% yield) as a clear oil. C₁₅H₂₂N₂O₃ MS m/z: 279.

D. (2S, 6R)-4-(2,4-dimethoxy-benzyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

Triethylamine (0.4 mL, 2.8 mmol) and N-(benzyloxycarbonyloxy)-succinimide (1.04 g, 10 4.2 mmol) is added to a solution of the above crude amine (387 mg, 1.4 mmol) in 15 mL of methylene chloride. The reaction mixture is left to stir overnight. The residue after concentration is chromatographed on silica gel (30% ethyl acetate/hexane) to give (2S, 6R)-4-(2,4-dimethoxy-benzyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (450 mg, 78 % yield) as a clear oil.

E. (2S, 6R)-2,6-Dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

(2S,6R)-4-(2,4-Dimethoxy-benzyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (1.13 g, 2.74 mmol) is dissolved in 20 mL of acetonitrile. An aqueous solution of potassium persulfate (2.2 g, 8.23 mmol) and sodium phosphate (2.3 g, 16.5 mmol) in 12 mL of H₂O is added, and the resulting mixture is heated to 95-100 °C for two hours. After cooling to room 20 temperature, ethyl acetate (200 mL) is used to extract the aqueous layer and dried over magnesium sulfate. The residue after filtration and concentration is chromatographed (SiO₂, 60% ethyl acetate/hexane) to give (2S, 6R)-2,6-Dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (480 mg, 67 % yield) as a yellow oil.

EXAMPLE 60. (2S, 6RS)-4-(4-chloro-quinolin-7-ylmethyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

(2S,6RS)-2,6-Dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (380 mg, 1.45 mmol) is dissolved in 10 mL of THF and 1mL of DMF. Sodium hydride (60%, 72 mg, 3.14 mmol) is added at 0 °C and left to stir at room temperature for thirty minutes before 7-bromomethyl-4-chloro-quinoline (257 mg, 1.0 mmol) is added. The reaction is stirred for four 30 hours. Ethyl acetate is added to the mixture, and the reaction is quenched with 3 mL of H₂O. The two layers are separated and ethyl acetate (2x 30 ml) is used to extract before dried over magnesium sulfate. The residue after filtration and concentration is chromatographed on silica gel (60% EtOAc/Hexane) to give (2S, 6RS)-4-(4-chloro-quinolin-7-ylmethyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (417 mg, 95 % yield). C₂₂H₂₀ClN₃O₃ MS m/z: 438, 440.

EXAMPLE 61. (3S,5RS)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one and

EXAMPLE 62. (3S, 5R)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one and

EXAMPLE 63 (3S, 5S)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one.

(2S, 6RS)-4-(4-Chloro-quinolin-7-ylmethyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic

5 acid benzyl ester (417 mg, 1.0 mmol) is taken up in 7 mL of acetonitrile, and iodotrimethylsilane (0.43 mL, 3.0 mmol) is added. The resulting mixture is stirred for one hour at room temperature before quenched with methanol (1 mL). The residue after concentration is taken up in 2N hydrochloric acid (3 mL) and is extracted with ether (2x 30 mL). The aqueous layer is condensed to dryness and the residue is recrystallized from isopropanol and ether to give a mixture (1:4 ratio) of (3S, 5RS)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one as a yellow solid (290 mg). The two epimers are separated using a flash column (SiO₂, 1% triethylamine/3% methanol/methylene chloride). C₁₆H₁₈ClN₃O MS m/z: 304, 306. The minor isomer (3S, 5R)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one is (3S, 5R)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one while the major isomer is (3S, 5S)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one. Alternatively, (3S, 5R)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one and (3S, 5S)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one can be made via the same chemistry shown below from pure (2S, 6S)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester and (2S, 6RS)-4-(4-chloro-quinolin-7-ylmethyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester, respectively.

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Alternative synthesis of (3S, 5R)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one.

A. (2S, 6R)-4-(4-chloro-quinolin-7-ylmethyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

(2S, 6R)-2,6-Dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (750 mg, 2.86

25 mmol) is dissolved in 20 mL of THF and 2 mL of DMF. Sodium hydride (60%, 142.6 mg, 6.20 mmol) is added at 0 °C, and the reaction is left to stir at room temperature for thirty minutes at which time the 7-bromomethyl-4-chloro-quinoline (952 mg, 3.72 mmol) is added. The reaction is complete after stirring for four hours. Ethyl acetate (200 mL) is added to the mixture, and the reaction is quenched with 3 mL of H₂O. The two layers are separated, and ethyl acetate (2x 30 mL) is used to extract and dried over magnesium sulfate. The residue after filtration and concentration is chromatographed on silica gel (60% EtOAc/Hexane) to give (2S,6R)-4-(4-chloro-quinolin-7-ylmethyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (1.04 g, 83 %).

B. (3S, 5R)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one.

A 33 % solution of hydrogen bromide in acetic acid (10 mL) is added to (2S,6R)-4-(4-chloro-quinolin-7-ylmethyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (1.04 g, 2.38 mmol). The reaction is left to stir at room temperature for one hour. The reaction mixture is diluted with ethyl acetate and stirred vigorously to force the product to precipitate out 5 of solution. The ethyl acetate is decanted off and the precipitate is purified on a silica gel column (1 % triethylamine/3 % methanol/methylene chloride) to 582 mg (81% yield) of (3S,5R)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one as a white solid.

EXAMPLE 64. (3S, 5S)-1-(4-chloro-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,5-dimethyl-piperazine-2-one and

EXAMPLE 65. (3S, 5R)-1-(4-chloro-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,5-dimethyl-piperazine-2-one.

The crude (3S,5RS)-1-(4-chloro-quinolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one (69 mg, 0.20 mmol) obtained from above is dissolved in 1 mL of DMF. Potassium carbonate (76 mg, 0.60 mmol) is added followed by the addition of 2-(3-bromopropenyl)-5-chloro-thiophene 15 (56 mg, 0.24 mmol). The reaction is left to stir overnight. The potassium carbonate is filtered off, and the crude material is purified. The two epimers are separated at this stage by preparative thin layer chromatography (80 % EtOAc/hexane) to give a major epimer (3S, 5R)-1-(4-chloro-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,5-dimethyl-piperazine-2-one 20 (25 mg, 26% yield) and a minor epimer (3S, 5S)-1-(4-chloro-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,5-dimethyl-piperazine-2-one (7 mg, 7.5% yield).

EXAMPLE 66. 4-(2-Oxopiperazin-1-ylmethyl)benzamidine.

A. 4-(4-Cyanobenzyl)-3-oxopiperazine-1-carboxylic acid benzyl ester.

To a solution of 3-oxo-piperazine-1-carboxylic acid benzyl ester (3.0 g, 12.8 mmol) and 4-bromomethyl tolylnitrile (2.76 g, 14.1 mmol) in 135 mL of THF and 15 mL of DMF at 0°C is added a 60% dispersion in mineral oil of NaH (0.49 g, 12.8 mmol). After 5 hours, the solution is diluted with saturated NH₄Cl and EtOAc. The organic layer is washed with H₂O and saturated NaCl. The organic layer is dried over MgSO₄, filtered and concentrated. The crude product is 30 purified by column chromatography over silica gel eluting with 20% EtOAc/CH₂Cl₂. The title compound is obtained as a white solid (4.01 g, 11.4 mmol). ¹H NMR (CDCl₃, 300MHz) δ 7.62 (d, 2H), 7.39 (m, 7H), 5.14 (s, 2H), 4.68 (s, 2H), 4.27 (s, 2H), 3.73 (m, 2H), 3.30 (m, 2H).

B. 4-(4-Carbamimidoylbenzyl)-3-oxo-piperazine-1-carboxylic acid benzyl ester.

A solution of 4-(4-cyanobenzyl)-3-oxopiperazine-1-carboxylic acid benzyl ester (2.4 g, 35 6.87 mmol) in 30mL of pyridine and 3 ml of Et₃N is saturated with H₂S. The resulting mixture is

sealed and stirred for 16 hours. After this time, the solution is concentrated. The residue is dissolved in 30 mL of acetone and methyl iodide (19.4 g, 137 mmol) is added. The solution is refluxed for 2 hours. After this time, the solution is concentrated. The residue is dissolved in MeOH (40 mL) and NH₄OAc (5.0 g, 65 mol) is added. The solution is refluxed for 3 hours. After 5 this time, the solution is concentrated. The crude product is purified by RP-HPLC eluting in a gradient of CH₃CN to 60% CH₃CN/H₂O(0.1%TFA). The appropriate collected fractions are lyophilized to give the product as a white foam. MS (FAB) m/z 367, (M+H).

C. 4-(2-Oxopiperazin-1-ylmethyl)benzamidine.

To a solution of 4-(4-carbamimidoylbenzyl)-3-oxopiperazine-1-carboxylic acid benzyl ester (2.0 g, 5.0 mmol) in 40 mL of MeOH and 4 mL of AcOH is added 10% Pd/C (0.4 g). The atmosphere above the reaction is replaced by hydrogen. After 4 hours, the solution is filtered through a pad of Celite. The organic layer is concentrated. The resulting crude product is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1%TFA) to 40% CH₃CN/H₂O (0.1% TFA). The title compound is obtained as a white foam. ¹H NMR (d⁶-DMSO, 300 MHz) δ 15 9.3 (bs, 4H), 9.1 (bs, 2H), 7.83 (d, 2H), 7.42 (d, 2H), 4.78 (s, 2H), 3.80 (s, 2H), 3.44 (m, 2H), 3.32 (m, 2H).

EXAMPLE 67. 1-(2-Aminoquinolin-6-ylmethyl)piperazin-2-one.

A. 4-(2-Chloro-quinolin-6-ylmethyl)-3-oxo-piperazine-1-carboxylic acid benzyl ester.

To a solution of 3-oxopiperazine-1-carboxylic acid benzyl ester (4.65 g, 19.8 mmol) and 6-bromomethyl-2-chloroquinoline (5.40 g, 21.0 mmol) in 80 mL of a 3:1 mixture of THF:DMF at 20 0°C is added sodium hydride (0.81 g, 20.2 mmol, 60% mineral oil dispersion). The resulting mixture is stirred for 1 hour at 0°C then at room temperature for 18 hours. The reaction mixture is quenched with saturated NH₄Cl solution, then diluted with EtOAc. The organic layer is 25 washed sequentially with 1N HCl, water, saturated NaHCO₃ and saturated NaCl, then dried over MgSO₄, filtered and concentrated. The crude product is triturated in Et₂O/hexanes/EtOAc and filtered to afford the title compound (6.96 g, 17.0 mmol) as a white solid. ¹H NMR (CDCl₃, 300 MHz) δ 8.08 (d, 1H), 8.00 (d, 1H), 7.69 (s, 1H), 7.63 (dd, 1H), 7.41 (d, 1H), 7.35 (s, 5H), 5.15 (s, 2H), 4.78 (s, 2H), 4.28 (s, 2H), 3.70 (m, 2H), 3.32 (bs, 2H).

B. 4-(2-Phenoxyquinolin-6-ylmethyl)-3-oxopiperazine-1-carboxylic acid benzyl ester.

A mixture of phenol (15.1 g, 160 mmol) and 4-(2-chloroquinolin-6-ylmethyl)-3-oxopiperazine-1-carboxylic acid benzyl ester (6.60 g, 16.1 mmol) is melted together at 70°C until a homogeneous mixture is obtained. Potassium hydroxide (3.15 g, 56.1 mmol) is added and the resulting mixture is heated overnight at 120°C. After 24 hours, the brown/black residue 35 is cooled to room temperature, diluted with CH₂Cl₂ and stirred with 1N NaOH (100 mL) for 30

minutes. The two layers are separated and the aqueous layer is extracted with CH_2Cl_2 . The combined organic layers are washed with 1N NaOH, saturated NaCl, dried over Na_2SO_4 , filtered and concentrated. The crude title compound (6.92 g, 14.8 mmol) is obtained as a beige foam and used in the subsequent step without further purification.

5 ^1H NMR (CDCl_3 , 300 MHz) δ 8.07 (d, 1H), 7.76 (d, 1H), 7.63 (s, 1H), 7.50 (dd, 1H), 7.42 (m, 2H), 7.34 (m, 6H), 7.25 (m, 2), 7.09 (d, 1H), 5.14 (s, 2), 4.75 (s, 2H), 4.27 (s, 2H), 3.66 (m, 2H), 3.30 (bs, 2H).

C. 4-(2-Aminoquinolin-6-ylmethyl)-3-oxopiperazine-1-carboxylic acid benzyl ester

A mixture of ammonium acetate (18.7 g, 242 mmol) and 4-(2-phenoxyquinolin-6-ylmethyl)-3-oxopiperazine-1-carboxylic acid benzyl ester (6.92 g, 14.8 mmol) is heated overnight at 150°C. After 21 hours, an additional 3 g of ammonium acetate is added and the heating is continued. After 5 hours, the mixture is cooled to room temperature, diluted with CH_2Cl_2 and stirred with 1N NaOH (100 mL) for 30 minutes. The two layers are separated and the aqueous layer is extracted with CH_2Cl_2 . The combined organic layers are washed with 1N NaOH, saturated NaCl, dried over Na_2SO_4 , filtered and concentrated. The crude mixture of the title compounds (5.50 g, 14.1 mmol) is obtained as a beige foam and used in the subsequent step without further purification.

Major component (4-(2-aminoquinolin-6-ylmethyl)-3-oxopiperazine-1-carboxylic acid benzyl ester): ^1H NMR (CDCl_3 , 300 MHz) δ 7.86 (d, 1H), 7.63 (d, 1H), 7.48 (d, 1H), 7.45 (d, 1H), 7.35 (s, 5H), 6.74 (d, 1H), 5.14 (s, 2H), 4.79 (bs, 2H), 4.71 (s, 2H), 4.26 (s, 2H), 3.66 (s, 2H), 3.30 (s, 2H).

Minor component (3-oxo-4-(2-oxo-1,2-dihydroquinolin-6-ylmethyl)piperazine-1-carboxylic acid benzyl ester): ^1H NMR (CDCl_3 , 300 MHz) δ 7.75 (d, 1H), 7.48 (m, 2H), 7.37 (m, 6H), 6.70 (d, 1H), 5.14 (s, 2H), 4.66 (s, 2H), 4.26 (s, 2H), 3.66 (s, 2H), 3.30 (s, 2H).

D. 1-(2-Aminoquinolin-6-ylmethyl)piperazin-2-one.

To a solution of a mixture of 4-(2-aminoquinolin-6-ylmethyl)-3-oxopiperazine-1-carboxylic acid benzyl ester and 3-oxo-4-(2-oxo-1,2-dihydroquinolin-6-ylmethyl)piperazine-1-carboxylic acid benzyl ester (5.50 g, 14.1 mmol) in 100 mL of 10:1 MeOH/HOAc is added a catalytic amount of 10% palladium on activated carbon. The heterogenous mixture is hydrogenated at room temperature under a balloon of H_2 for 18 hours. The reaction mixture is filtered through a pad of Celite, washed with MeOH, and the filtrate is concentrated in vacuo. The crude mixture of products is purified by RP-HPLC eluting in a gradient of 2% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (0.1% TFA) to 20% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (0.1% TFA) and the appropriate product fractions are concentrated in vacuo to provide 1-(2-aminoquinolin-6-ylmethyl)-piperazin-2-one trifluoroacetate (2.64 g, 5.45 mmol) as the major product in the form of a white solid. ^1H NMR

(d⁶-DMSO, 300 MHz) δ 8.78 (bs, 2H), 8.31 (d, 1H), 7.80 (s, 1H), 7.66 (m, 2H), 7.08 (d, 1H), 4.70 (s, 2H), 3.84 (s, 2H), 3.46 (bs, 4H). MS m/z 256, [M+]. Elemental analysis calculated with 0.25 mol of H₂O cal. C=44.25%, H=3.82%, N=11.47%, found C=44.23%, H=3.76%, N=11.23%. The minor by-product 6-(2-oxo-piperazin-1-ylmethyl)-1H-quinolin-2-one (0.62 g, 1.28 mmol) is also isolated from the RP-HPLC separation as a white solid ¹H NMR (d⁶-DMSO, 300 MHz) δ 11.76 (bs, 1H), 9.30 (bs, 2H), 7.85 (d, 1H), 7.55 (s, 1H), 7.42 (d, 1H), 7.28 (d, 1H), 6.50 (d, 1H), 4.60 (s, 2H), 3.80 (s, 2H), 3.38 (bs, 4H). MS m/z 257, [M+]. Elemental analysis calculated with 0.5 mol of H₂O cal. C=43.72%, H=3.68%, N=8.50%, found C=43.70%, H=3.62%, N=8.61%.

10 EXAMPLE 68. 1-(1-Aminoisoquinolin-6-ylmethyl)piperazin-2-one.

The title compound is prepared as described in EXAMPLE 67 substituting 6-bromomethyl-1-chloroisooquinoline for bromomethyl-2-chloroquinoline. ¹H NMR (d⁶-DMSO, 300 MHz) δ 9.18 (bs, 2H), 8.53 (d, 1H), 7.81 (s, 1H), 7.63 (m, 2H), 7.14 (d, 1H), 4.77 (s, 2H), 3.88 (s, 2H), 3.50 (m, 4H).

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EXAMPLE 69. 2-(2-Oxopiperazin-1-ylmethyl)pyrrolo[3,2-c]pyridin-1-carboxylic acid tert-butyl ester.

A. 3-Iodopyridin-4-ylamine.

A solution of potassium iodide (19.48 g, 117.4 mmol) and iodine (18.37 g, 72.3 mmol) in water (77 mL) is added dropwise via an addition funnel to a refluxing solution of 4-aminopyridine (9.21 g, 97.8 mmol) and sodium carbonate (6.12 g, 57.7 mmol) in water (35 mL). Upon complete addition the mixture is stirred for 2 hours at reflux then cooled to room temperature and extracted with ethyl acetate. The combined organic layers are washed with saturated sodium thiosulfate solution (3x) and brine then dried over MgSO₄, filtered and concentrated to give the title product (8.37 g, 38.0 mmol) and a trace of the di-iodo compound as an yellow/orange solid. This material is used in the subsequent step without further purification. ¹H NMR (CDCl₃, 300 MHz) δ 8.70 (s, 1H), 8.10 (d, 1H), 6.55 (d, 1H), 4.60 (bs, 2H).

B. (3-Iodopyridin-4-yl)-carbamic acid tert-butyl ester.

Di-tert-butyl dicarbonate (20.7 g, 94.8 mmol) is added to a solution of 3-iodopyridin-4-ylamine (19.0 g, 86.4 mmol) in THF (86 mL). The resulting solution is stirred for 2 hours at room temperature then concentrated. The residue is diluted with ethyl acetate and washed with saturated sodium bicarbonate solution and brine. The organic layer is dried over MgSO₄, filtered and concentrated. The residue is purified by column chromatography eluting with 1% EtOAc/CH₂Cl₂ to give the title product and a small amount of the BOC-protected di-iodo compound. Trituration of the mixture with ether/hexane removes the undesired compound

leaving the title product in the solution. Filtration of the solid and concentration of the filtrate yields the title product (18.95 g, 59.2 mmol). ^1H NMR (CDCl_3 , 300 MHz) δ 8.75 (s, 1H), 8.35 (d, 1H), 8.1 (d, 1H), 7.0 (bs, 1H), 1.55 (s, 9H).

C. 3-Oxo-4-prop-2-ynylpiperazine-1-carboxylic acid benzyl ester.

5 Sodium hydride (0.82 g, 23.0 mmol, 60% mineral oil dispersion) is added to a solution of 4-benzyloxycarbonylpiperazin-2-one (5.13 g, 21.9 mmol) in THF/DMF (75 mL, 3/1 v/v) at 0°C. The mixture is stirred for 5 minutes, then propargyl bromide (3.7 mL, 41.5 mmol) is added dropwise. The resulting solution is stirred for 1 hour then brought to room temperature and stirred for 2 hours. The reaction is quenched with saturated ammonium chloride solution then 10 diluted with ethyl acetate and washed with water (4x) and brine. The organic layer is dried over MgSO_4 , filtered and concentrated to dryness. The residue is purified by column chromatography eluting with 5% MeOH/ CH_2Cl_2 to give the product (5.96 g, 21.9 mmol) as a white solid. ^1H NMR (CDCl_3 , 300 MHz) δ 7.3 (m, 5H), 5.12 (s, 2H), 4.25 (s, 2H), 4.16 (s, 2H), 3.75 (m, 2H), 3.47 (m, 2H), 2.22 (s, 1H).

15 D. 2-(4-Benzylloxycarbonyl-2-oxopiperazin-1-ylmethyl)pyrrolo[3,2-c]pyridin-1-carboxylic acid tert-butyl ester.

Pd(PPh_3)₂Cl₂ (0.29 g, 0.41 mmol), Cul (0.05 g, 0.25 mmol) and triethylamine (4.6 mL, 32.9 mmol) is added to a solution of 3-oxo-4-prop-2-ynylpiperazine-1-carboxylic acid benzyl ester (2.24 g, 8.23 mmol) and (3-iodopyridin-4-yl)-carbamic acid tert-butyl ester (2.63 g, 8.23 mmol) in DMF (30 mL) at room temperature. The mixture is heated to 100°C and stirred for 1.5 hours. The reaction mixture is then cooled to 50°C and DBU (2.5 mL, 16.5 mmol) is added. After 30 minutes the solution is cooled to room temperature, diluted with ethyl acetate and washed with saturated ammonium chloride, water and brine. The organic layer is dried over MgSO_4 , filtered and concentrated in vacuo. The resulting solid is purified by column 20 chromatography eluting with a gradient of 2% MeOH/ CH_2Cl_2 to 5% MeOH/ CH_2Cl_2 to give the product (2.93 g, 6.31 mmol) as a white solid. ^1H NMR (CDCl_3 , 300 MHz) δ 8.75 (s, 1H), 8.4 (d, 1H), 7.85 (d, 1H), 7.35 (m, 5H), 6.38 (s, 1H), 5.2 (s, 2H), 5.00 (s, 2H), 4.29 (s, 2H), 3.85 (m, 2H), 3.52 (m, 2H), 1.7 (s, 9H). Ion spray MS, $[\text{M}+\text{H}]^+ = 465$.

E. 2-(2-Oxopiperazin-1-ylmethyl)pyrrolo[3,2-c]pyridin-1-carboxylic acid tert-butyl ester.

30 Palladium black (1.1 g, 10.3 mmol) is added to a solution of 2-(4-benzyloxycarbonyl-2-oxo-piperazin-1-ylmethyl)pyrrolo[3,2-c]pyridin-1-carboxylic acid tert-butyl ester (1.7 g, 3.7 mmol) in $\text{HCO}_2\text{H}/\text{MeOH}$ (45 mL, 4.4% solution). After 40 minutes the catalyst is filtered through Celite and washed with MeOH. The filtrate is concentrated in vacuo to remove methanol then the resulting solution is diluted with methylene chloride and washed with saturated sodium bicarbonate, and brine. The organic layer is dried over MgSO_4 , filtered and concentrated to

dryness. The resulting solid is purified by column chromatography eluting with a gradient of 5% MeOH/CH₂Cl₂ to 10% MeOH/CH₂Cl₂ to give the product (0.8 g, 2.5 mmol) as a pale yellow foamy solid. ¹H NMR (CDCl₃, 300 MHz) δ 8.78 (s, 1H), 8.40 (d, 1H), 7.9 (d, 1H), 6.48 (s, 1H), 4.98 (s, 2H), 3.7 (s, 2H), 3.51 (t, 2H), 3.40 (t, 2H), 1.91 (bs, 1H), 1.70 (s, 9H).

5

EXAMPLE 70. 2-(5-(±)-Methoxycarbonyl-2-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester.

A. 2-Benzylloxycarbonylamino-3-(prop-2-ynylamino)-propionic acid methyl ester.

Propargyl bromide (1.6 mL, 14.4 mmol) is added to a solution of 3-amino-2-

10 benzylloxycarbonylamino-propionic acid methyl ester hydrochloride (4.0 g, 13.9 mmol) and triethylamine (4.1 mL, 29.4 mmol) in THF (46 mL). The resulting mixture is heated to 50°C and stirred overnight then cooled to RT and concentrated in vacuo. The crude residue is diluted with methylene chloride, washed with saturated NaHCO₃ and brine then the organic layer is dried over MgSO₄, filtered and concentrated in vacuo. The crude material (4.0 g) is taken on to 15 the subsequent step without further purification. ¹H NMR (CDCl₃, 300 MHz) δ 7.25-7.30 (m, 5H), 5.75 (bs, 1H), 5.20 (s, 2H), 4.45 (bs, 1H), 3.80 (s, 3H), 3.75 (m, 1H), 3.31 (s, 2H), 3.08 (dd, 1H), 2.98 (dd, 1H), 2.20 (t, 1H). EI MS, [M+H]⁺=291.

B. 2-Benzylloxycarbonylamino-3-(bromoacetyl-prop-2-ynyl-amino)-propionic acid methyl ester.

DCC (2.27 g, 11.0 mmol) and bromoacetic acid (1.48 g, 10.7 mmol) is added to a

20 solution of 2-benzylloxycarbonylamino-3-(prop-2-ynylamino)-propionic acid methyl ester (3.10 g, 10.7 mmol) in CH₂Cl₂ at RT. The mixture is stirred overnight then diluted with ether. The white solid which precipitates out is filtered and the filtrate is concentrated to give a yellow oil. The crude product is purified by chromatography eluting with a gradient of 40% EtOAc/hexanes to 50% EtOAc/hexanes to yield the title product (2.1g, 5.12 mmol) as an oil. ¹H NMR (CDCl₃, 300 MHz) δ 7.30 (m, 5H), 5.70 (d, 1H), 5.10 (s, 2H), 4.63 (m, 1H), 4.15 (d, 2H), 4.00 (m, 1H), 3.80 (s, 3H), 3.75 (s, 2H), 3.70 (dd, 1H), 2.27 (bs, 1H). Ion spray MS, [M+H]⁺=411, 413, Br pattern.

C. 5-Oxo-4-prop-2-ynyl-piperazine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester.

Sodium hydride (0.20 mg, 4.9 mmol) is added to a solution of 2-

30 benzylloxycarbonylamino-3-(bromoacetyl-prop-2-ynyl-amino)-propionic acid methyl ester (2.0 g, 4.8 mmol) in THF (50 mL) at 0°C. The solution is stirred for 40 minutes then quenched with saturated NH₄Cl solution. The reaction mixture is concentrated in vacuo then diluted with CH₂Cl₂ and washed with brine. The organic layer is dried over, filtered and concentrated in vacuo. The crude product is purified by chromatography eluting with 50% EtOAc/hexanes to 35 give the title product (1.4 g, 4.1 mmol). ¹H NMR (CDCl₃, 300 MHz) δ 7.30 (m, 5H), 5.20 (s, 2H),

5.10 (m, 1H), 4.30 (dd, 1H), 4.25 (d, 2H), 4.08 (m, 1H), 4.00 (dd, 1H), 3.78 (dd, 1H), 3.78 (s, 3H), 2.25 (t, 1H).

5 D. 2-(5-(\pm)-Methoxycarbonyl-2-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester.

¹H NMR (CDCl₃, 300 MHz) δ 8.75 (s, 1H), 8.41 (d, 1H), 7.90 (d, 1H), 6.42 (s, 1H), 5.00 (AB, 2H), 3.85-3.93 (m, 2H), 3.78 (s, 3H), 3.70-3.81 (m, 3H), 1.65 (s, 9H). Ion spray MS, [M+H]⁺=389.

10 EXAMPLE 71. 2-(2-(\pm)-Methoxycarbonyl-6-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester.

¹H NMR (CDCl₃, 300 MHz) δ 8.81 (s, 1H), 8.43 (d, 1H), 7.90 (d, 1H), 6.48 (s, 1H), 5.63 (d, 1H), 4.40 (d, 1H), 4.20 (m, 1H), 3.78 (s, 3H), 3.70 (d, 1H), 3.52 (d, 1H), 3.33 (dd, 1H), 2.92 (s, 1H), 1.55 (s, 9H). Ion spray MS, [M+H]⁺=389.

15

EXAMPLE 72. 1-(4-Aminoquinazoline-7-ylmethyl)piperazine-2-one.

A. 4-(4-Chloroquinazoline-7-ylmethyl)-3-oxopiperazine-1-carboxylic acid tert-butyl ester.

To a solution of 3-oxopiperazine-1-carboxylic acid tert-butyl ester (3.93 g, 19.6 mmol) and 7-bromomethyl-4-chloroquinazoline, EXAMPLE 7, (5.0 g, 19.6 mmol) in 150 mL of THF and

20 15 mL of DMF at 0°C is added a 60% dispersion in mineral oil of NaH (0.79 g, 19.6 mmol). The solution is stirred at 0°C for 0.5 hours and then is allowed to warm to ambient temperature. After 4 hours, the solution is poured into a saturated solution of NH₄Cl. The layers are separated and the organic layer is washed with H₂O, and saturated NaCl, dried over MgSO₄, filtered and concentrated. The title compound is obtained as a white solid (5.1 g, 13.4 mmol).

25 MS (FAB) m/z 377, 379, (M+H), chlorine pattern.

B. 4-(4-Aminoquinazoline-7-ylmethyl)-3-oxopiperazine-1-carboxylic acid tert-butyl ester.

A solution of 4-(4-chloroquinazoline-7-ylmethyl)-3-oxopiperazine-1-carboxylic acid tert-butyl ester (1.84 g, 4.9 mmol) in 120 mL of ethanol is saturated with NH₃ gas. To the resulting solution is added acetic acid (0.03 mL). The solution is heated to reflux. After 16 hours, the solution is concentrated. The resulting solid is dissolved in CH₂Cl₂ and the inorganic salts are filtered off. The organic solution is concentrated. The resulting solid is triturated with EtOAc. The title compound is obtained as a white solid (1.59 g, 4.5 mmol). MS (FAB) m/z 356, (M+H).

C. 1-(4-Aminoquinazoline-7-ylmethyl)piperazine-2-one.

A solution of 4-(4-aminoquinazoline-7-ylmethyl)-3-oxo-piperazine-1-carboxylic acid tert-butyl ester (1.92 g, 5.4 mmol) in EtOAc (200 mL) at 0 °C is saturated with HCl gas. The

solution is stirred at 0°C for 4 hours. After this time, the solution is concentrated. The title compound is obtained as a white solid (1.79 g, 5.4 mmol). ^1H NMR ($\text{d}^6\text{-DMSO}$, 300 MHz) δ 9.9 (bs, 3H), 9.7 (bs, 2H), 8.8 (s, 1H), 8.46 (d, 1H), 7.72 (s, 1H), 7.61 (d, 1H), 4.78 (s, 2H), 3.83 (s, 2H), 3.4 (m, 4H).

5

Example 73. 1-(4-Amino-thieno[2,3-d]pyrimidin-6-ylmethyl)-piperazin-2-one.

A. 1-(4-Amino-thieno[2,3-d]pyrimidin-6-ylmethyl)-3-oxo-piperazine-1-carboxylic acid tert-butyl ester.

10 The title compound is prepared as described in EXAMPLE 72, Part A, substituting 6-bromomethyl-4-chlorothieno[2,3-d]pyrimidine for 7-bromomethyl-4-chloroquinazoline.

Followed by treatment as described in EXAMPLE 72, Part B, the title compound is obtained.

^1H NMR (CD_3OD , 300 MHz) δ 8.22 (s, 1H), 7.35 (s, 1H), 5.48 (s, 2H), 4.10 (s, 2H), 3.60 (m, 2H), 3.40 (m, 2H), 1.45 (s, 9H). MS (ion spray), 364, ($\text{M}+\text{H}$).

15 B. 1-(4-Amino-thieno[2,3-d]pyrimidin-6-ylmethyl)-piperazin-2-one.

The title compound is obtained by treatment of 1-(4-amino-thieno[2,3-d]pyrimidin-6-ylmethyl)-3-oxo-piperazine-1-carboxylic acid tert-butyl ester as described in EXAMPLE 72, Part C. MS (EI), 2634, (M^+).

20 EXAMPLE 74. 4-[3-(2-Oxo-piperazin-1-yl)-propyl]-piperidine-1-carboxylic acid tert-butyl ester.

A. 4-[3-(1-tert-butoxycarbonyl-piperidin-4-yl)-propyl]-3-oxo-piperazine-1-carboxylic acid benzyl ester.

The title compound is prepared as described in EXAMPLE 72, Part A, substituting 3-oxopiperazine-1-carboxylic acid benzyl ester for 3-oxopiperazine-1-carboxylic acid tert-butyl ester and 4-(3-bromopropyl)-piperidine-1-carboxylic acid tert-butyl ester for 7-bromomethyl-4-chloroquinazoline. The title compound is obtained as a white foam. ^1H NMR (CDCl_3 , 300 MHz) δ 7.38 (m, 5H), 5.12 (s, 2H), 4.18 (m, 4H), 3.73 (m, 2H), 3.33 (m, 4H), 2.66 (m, 2H), 1.58 (m, 6H), 1.42 (s, 9H), 1.38 (m, 3H).

B. 4-[3-(2-Oxo-piperazin-1-yl)-propyl]-piperidine-1-carboxylic acid tert-butyl ester.

30 4-[3-(1-tert-butoxycarbonyl-piperidin-4-yl)-propyl]-3-oxo-piperazine-1-carboxylic acid benzyl ester is treated as described in EXAMPLE 67, Part D, to give the title compound as an oil.

EXAMPLE 75. 1-(4-Amino-quinazoline-7-ylmethyl)-3-methoxymethyl-piperazine-2-one.

35 A. 2-Methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

To a solution of 2-oxo-3-(S)-methoxymethylpiperidine (5.36g, 19.3mmol), EXAMPLE 41, in 200mL of 10:1 THF:DMF is added 2-(benzhydrylidene-amino)-4-bromomethyl-benzonitrile (12.6g, 60% purity, 19.3mmol), prepared as in EXAMPLE 13. The solution is cooled to 0°C. To the solution is added NaH (0.77g of a 60% dispersion in mineral oil, 19.3mmol). The solution is stirred for 16 hours. After this time, 1N HCl is added until the pH=1. The solution is stirred for 1 hour. After this time, the solution is diluted with EtOAc. The organic layer is washed with water and sat. NaCl. The organic layer is dried over MgSO₄, filtered and concentrated under vacuum. The resulting crude product is purified by column chromatography eluting with a gradient of 20%EtOAc/CH₂Cl₂ to 40%EtOAc/CH₂Cl₂. The title compound (6.8g, 16.7mmol) is obtained as a white solid. ¹H NMR (CDCl₃, 300MHz) δ 7.34 (m, 5H), 6.61 (m, 2H), 5.13 (AB, 2H), 4.76 (m, 1H), 4.40 (AB, 2H), 4.08 (m, 5H), 3.74 (m, 2H), 3.32 (m, 1H), 3.30 (s, 3H), 3.10 (m, 1H).

B. 4-(4-Amino-quinazolin-7-ylmethyl)-2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

To a solution of 2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester

(6.8g, 16.7mmol) in 100mL of ethanol is added triazine (2.2g, 26.4mmol) and acetic acid (1.6g, 26.4mmol). The solution is heated to a reflux. After 36h, the solution is concentrated. The resulting crude product is purified by column chromatography eluting with a gradient of 2%MeOH/CH₂Cl₂ to 5% MeOH/CH₂Cl₂. The title compound (5.8g, 13.3mmol) is obtained as a white solid. ¹H NMR (CDCl₃, 300MHz) δ 8.55 (s, 1H), 7.72 (m, 2H), 7.48 (m, 1H), 7.35 (m, 5H), 6.40 (bs, 2H), 5.16 (AB, 2H), 5.06 (m, 1H), 4.72 (m, 1H), 4.59 (m, 1H), 4.09 (m, 2H), 3.74 (m, 2H), 3.44 (m, 1H), 3.30 (s, 3H), 3.12 (m, 1H). MS (ion spray) m/z 436, (M+H).

C. 1-(4-Amino-quinazoline-7-ylmethyl)-3-methoxymethyl-piperazine-2-one.

To a solution of 2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (5.8g, 13.3mmol) in 50mL of acetic acid is added dropwise, 20mL of a 30%HBr in AcOH solution. The solution is stirred for 1 hour. After this time, the solution is concentrated. The resulting crude product is purified by column chromatography eluting with CH₂Cl₂:MeOH:NH₄OH (20:5:1). The title compound (2.0g, 6.6mmol) is obtained as a white solid. ¹H NMR (d⁶-DMSO, 300MHz) δ 8.60 (s, 1H), 7.72 (m, 2H), 7.48 (d, 1H), 5.60 (bs, 2H), 4.72 (AB, 2H), 3.87 (m, 2H), 3.71 (m, 1H), 3.42 (m, 1H), 3.40 (s, 3H), 3.19 (m, 2H), 3.02 (m, 1H). MS (ion spray) m/z 302, (M+H).

30

EXAMPLE 76. 1-(4-Aminoquinazoline-7-ylmethyl)-3-butyl-piperazine-2-one.

The title compound is prepared as described in EXAMPLE 75, substituting 2-butyl-3-oxo-piperazine-1-carboxylic acid benzyl ester, Example 42, for 2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester. ¹H NMR (CD₃OD, 300MHz) δ 8.35 (s, 1H), 8.09 (d,

1H), 7.54 (s, 1H), 7.41 (d, 1H), 4.74 (s, 2H), 3.43 (m, 2H), 3.28 (m, 1H), 3.09 (m, 1H), 2.95 (m, 1H), 1.92 (m, 1H), 1.70 (m, 1H), 1.39 (m, 4H), 0.93 (m, 3H). MS (ion spray) m/z 314, (M+H).

EXAMPLE 77. 1-(4-Aminoquinazoline-7-ylmethyl)-3-ethyl-piperazine-2-one.

5 The title compound is prepared as described in EXAMPLE 75, substituting 2-ethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester r, Example 43, for 2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester. ^1H NMR (CD₃OD, 300MHz) δ 8.36 (s, 1H), 8.11 (d, 1H), 7.57 (s, 1H), 7.42 (d, 1H), 4.78 (s, 2H), 3.40 (m, 2H), 3.29 (m, 1H), 3.11 (m, 1H), 2.98 (m, 1H), 2.00 (m, 1H), 1.77 (m, 1H), 1.20 (m, 3H). MS (ion spray) m/z 286, (M+H).

10

EXAMPLE 78. 1-(4-Aminoquinazoline-7-ylmethyl)-3-propyl-piperazine-2-one.

15 The title compound is prepared as described in EXAMPLE 75, substituting 2-propyl-3-oxo-piperazine-1-carboxylic acid benzyl ester, Example 44, for 2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester. ^1H NMR (CD₃OD, 300MHz) δ 8.36 (s, 1H), 8.13 (d, 1H), 7.60 (s, 1H), 7.47 (d, 1H), 4.78 (s, 2H), 3.44 (m, 2H), 3.30 (m, 1H), 3.11 (m, 1H), 2.97 (m, 1H), 1.98 (m, 1H), 1.72 (m, 1H), 1.50 (m, 2H), 0.97 (m, 3H). MS (ion spray) m/z 300, (M+H).

EXAMPLE 79. 1-(4-Amino-quinazoline-7-ylmethyl)-3-ethoxymethyl-piperazine-2-one.

20 The title compound is prepared as described in EXAMPLE 75, substituting 2-ethoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester, Example 45, for 2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester. ^1H NMR (CD₃OD, 300MHz) δ 8.34 (s, 1H), 8.07 (d, 1H), 7.53 (s, 1H), 7.40 (d, 1H), 4.79 (AB, 2H), 3.90 (m, 1H), 3.72 (m, 1H), 3.68 (m, 1H), 3.52 (m, 2H), 3.36 (m, 2H), 3.20 (m, 1H), 3.00 (m, 1H), 1.92 (m, 3H). MS (ion spray) m/z 316, (M+H).

25

EXAMPLE 80. 1-(4-Amino-quinazoline-7-ylmethyl)-3-methyl-piperazine-2-one.

30 The title compound is prepared as described in EXAMPLE 75, substituting 2-methyl-3-oxo-piperazine-1-carboxylic acid benzyl ester, Example 46, for 2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester. ^1H NMR (CD₃OD, 300MHz) δ 8.36 (s, 1H), 8.11 (d, 1H), 7.57 (s, 1H), 7.44 (d, 1H), 4.79 (AB, 2H), 3.58 (m, 1H), 3.47 (m, 1H), 3.31 (m, 1H), 3.12 (m, 1H), 3.00 (m, 1H), 1.41 (d, 3H). MS (ion spray) m/z 272, (M+H).

EXAMPLE 81. 1-(4-Amino-quinazoline-7-ylmethyl)-3-benzyl-piperazine-2-one.

35 The title compound is prepared as described in EXAMPLE 75, substituting 2-benzyl-3-oxo-piperazine-1-carboxylic acid benzyl, Example 47, ester for 2-methoxymethyl-3-oxo-

piperazine-1-carboxylic acid benzyl ester. ^1H NMR (CD₃OD, 300MHz) δ 8.35 (s, 1H), 8.09 (d, 1H), 7.57 (s, 1H), 7.38 (d, 1H), 7.27 (m, 5H), 4.74 (AB, 2H), 3.76 (m, 1H), 3.47 (m, 1H), 3.30 (m, 3H), 3.08 (m, 1H), 2.96 (m, 1H). MS (ion spray) m/z 348, (M+H).

5 **EXAMPLE 82. 1-(4-Amino-quinazoline-7-ylmethyl)-3-(1-methoxyethyl)-piperazine-2-one.**

The title compound is prepared as described in EXAMPLE 75, substituting 2-(1-methoxyethyl)-3-oxo-piperazine-1-carboxylic acid benzyl ester, Example 48, for 2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester. This compound is isolated as the bis hydrobromide salt. ^1H NMR (CD₃OD, 300MHz) δ 8.70 (s, 1H), 8.40 (d, 1H), 7.88 (s, 1H), 7.71 (d, 1H), 4.94 (AB, 2H), 4.30 (m, 2H), 3.76 (m, 1H), 3.68 (m, 3H), 3.36 (s, 3H), 1.42 (d, 3H). MS (ion spray) m/z 316, (M+H).

EXAMPLE 83. 1-(4-Amino-quinazoline-7-ylmethyl)-3,3-dimethyl-piperazine-2-one.

The title compound is prepared as described in EXAMPLE 75, substituting 2,2-dimethyl-15 3-oxo-piperazine-1-carboxylic acid benzyl ester, Example 49, for 2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester. ^1H NMR (d⁶-DMSO, 300MHz) δ 8.34 (s, 1H), 8.12 (d, 1H), 7.72 (bs, 2H), 7.41 (s, 1H), 7.26 (d, 1H), 4.60 (s, 2H), 3.33 (m, 2H), 2.98 (m, 2H), 1.27 (s, 6H).

20 **EXAMPLE 84. 1-(4-Amino-quinazoline-7-ylmethyl)-3-isopropyl-piperazine-2-one.**

The title compound is prepared as described in EXAMPLE 75, substituting 2-isopropyl-3-oxo-piperazine-1-carboxylic acid benzyl ester, Example 50, for 2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester. ^1H NMR (d⁶-DMSO, 300MHz) δ 8.32 (s, 1H), 8.12 (d, 1H), 7.66 (bs, 2H), 7.42 (s, 1H), 7.27 (d, 1H), 4.60 (AB, 2H), 3.23 (m, 2H), 3.05(m, 1H), 2.79 (m, 1H), 2.34 (m, 1H), 0.92 (s, 3H), 0.80 (s, 3H).

EXAMPLE 85. 1-(4-Amino-quinazoline-7-ylmethyl)-3-isobutyl-piperazine-2-one.

The title compound is prepared as described in EXAMPLE 75, substituting 2-isobutyl-3-oxo-piperazine-1-carboxylic acid benzyl ester, Example 51, for 2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester. ^1H NMR (d⁶-DMSO, 300MHz) δ 8.65 (s, 1H), 7.70 (m, 2H), 7.48 (m, 1H), 5.61 (m, 2H), 4.82 (m, 1H), 4.65 (m, 1H), 3.52 (dd, 1H), 3.37 (m, 1H), 3.18 (m, 2H), 2.98 (m, 1H), 1.92 (m, 1H), 1.76 (m, 1H), 1.59 (m, 2H), 0.95 (m, 6H).

EXAMPLE 86. 1-(4-Amino-quinazoline-7-ylmethyl)-3-(2-methoxyethyl) 1-piperazine-2-one.

The title compound is prepared as described in EXAMPLE 75, substituting 2-(2-methoxyethyl)-3-oxo-piperazine-1-carboxylic acid benzyl ester, Example 52, for 2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester. ^1H NMR ($\text{d}^6\text{-DMSO}$, 300MHz) δ 8.32 (s, 1H), 8.13 (d, 1H), 7.70 (bs, 2H), 7.42 (s, 1H), 7.28 (m, 1H), 4.60 (m, 2H), 3.32 (m, 8H), 3.11 (m, 1H), 2.95 (m, 1H), 2.78 (m, 1H), 2.07 (m, 1H), 1.72 (m, 1H).

EXAMPLE 87. 1-(4-Amino-quinazoline-7-ylmethyl)-3-methoxymethyl-6-methyl-piperazine-2-one.

The title compound is prepared as described in EXAMPLE 75, substituting 2-methoxymethyl-5-methyl-3-oxo-piperazine-1-carboxylic acid benzyl ester, Example 53, for 2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester. ^1H NMR (CD_3OD , 300MHz) δ 8.72 (s, 1H), 8.32 (d, 1H), 7.78 (m, 2H), 5.11 (m, 1H), 4.81 (m, 1H), 4.42 (m, 1H), 4.13 (m, 1H), 4.04 (m, 1H), 3.74 (m, 2H), 3.52 (m, 1H), 3.43 (s, 3H), 1.34 (d, 3H).

EXAMPLE 88. (3S,5RS)-1-(4-amino-quinazolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one.

A. (2S,6RS)-4-[3-(benzhydryl-amino)-4-cyano-benzyl]-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

To a solution of the (2S,6RS)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (1.98 g, 7.56 mmol) in 20 mL of tetrahydrofuran and 2 mL of DMF is added sodium hydride (60%, 289 mg, 12.6 mmol) at 0°C. The reaction is stirred for one hour at room temperature and the 2-benzhydrylidene-amino)-4-bromomethyl-benonitrile (4.24 mg, 11.34 mmol), Example 13, is added. After stirring at room temperature overnight, the tetrahydrofuran is removed. The residue is taken up in ethyl acetate. Excess sodium hydride is quenched with 5 mL of water, and normal aqueous work-up followed. The crude product is chromatographed on silica gel (50% EtOAc/Hexane) to give (2S,6RS)-4-[3-(benzhydryl-amino)-4-cyano-benzyl]-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (2.6 g, 65%). $\text{C}_{35}\text{H}_{32}\text{N}_4\text{O}_3$ MS m/z: 557.

B. (2S,6RS)-4-(3-amino)-4-cyano-benzyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

(2S,6RS)-4-[3-(Benzhydryl-amino)-4-cyano-benzyl]-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (2.6 g, 5.21 mmol) is dissolved in 100 mL of ethyl acetate and cooled to 0°C. A 12N solution of hydrochloric acid (0.5 ml, 6.0 mmol) is added dropwise. The deprotection is complete in thirty minutes. The reaction mixture is washed with 10 % sodium bicarbonate. The ethyl acetate layer is dried with magnesium sulfate, filtered and condensed. The resulting residue is purified by flash column (SiO_2 , 60 % ethyl acetate/hexane) to give the

product (2S,6RS)-4-(3-amino)-4-cyano-benzyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (2.03 g, 99 %).

C. (2S,6RS)-4-(4-Amino-quinazolin-7-ylmethyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester.

5 Glacial acetic acid (0.9 ml, 15.54 mmol) and 1,3,5-triazine (840 mg, 10.36 mmol) is added to a solution of (2S,6RS)-4-(3-amino-4-cyano-benzyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (2.03 g, 5.18 mmol) in ethanol. The resulting mixture is heated to reflux overnight. Replaced the ethanol with ethyl acetate and washed with saturated sodium bicarbonate (5 mL). The ethyl acetate layer is dried with magnesium sulfate, filtered and
10 condensed. The resulting residue is purified by flash column (SiO₂, 20% methanol/methylene chloride) to give the product (2S,6RS)-4-(4-amino-quinazolin-7-ylmethyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (1.85 g, 85%) as a yellow solid. C₂₃H₂₅N₅O₃ MS m/z: 420.

D. (3S,5RS)-1-(4-Amino-quinazolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one.

15 Palladium on carbon (10 %, 700 mg) is added to a solution of (2S,6RS)-4-(4-amino-quinazolin-7-ylmethyl)-2,6-dimethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester (1.62 g, 3.87 mmol) in 20 mL of methanol and 2 mL of acetic acid. The reaction mixture is left to stir in an atmosphere of hydrogen for eight hours. The palladium is filtered off, and the volatile solvents are removed on the rotovap. The crude product (1.7 g, 95 %) is isolated as a white
20 solid. The two epimers are separated on silica gel (1% triethylamine/15% methanol/methylene chloride). The minor epimer is assigned as (3S,5R)-1-(4-amino-quinazolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one and the major epimer is assigned as (3S,5S)-1-(4-amino-quinazolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one.

25 EXAMPLE 89. 1-(4-Chloroquinolin-7-ylmethyl)-piperazin-2-one.

4-(Benzylloxycarbonyl)-piperazin-2-one (1.1 g, 4.6 mmol) is dissolved in THF (50 mL), cooled in an ice bath and treated with tetrabutylammonium iodide (0.18 g, mmol) and 60% sodium hydride (0.24 g, 6.0 mmol). The reaction mixture is stirred at 0 C for 30 minutes then treated dropwise with a solution of 7-bromomethyl-4-chloroquinoline (1.2 g, 4.6 mmol),
30 Example 14, in THF (50 mL). The resulting solution is stirred at 0 C for 2 h then quenched with ammonium chloride solution and concentrated. Dilution with ethyl acetate is followed by a water wash; the organic layer is dried (sodium sulfate) and concentrated. The residue is chromatographed (4% methanol/methylene chloride) to yield solid 4-(benzylloxycarbonyl)-1-(4-chloroquinolin-7-ylmethyl)-piperazin-2-one (1.2 g, 2.9 mmol). A
35 portion of this material (0.75 g, 1.8 mmol) is dissolved in acetonitrile (20 mL) and treated with

iodo trimethylsilane (0.78 mL, 5.4 mmol) at room temperature for 3 hours. The reaction is quenched with methanol and concentrated to dryness. Methanol addition and concentration is repeated four times. The final residue is taken up in 2M aqueous HCl; the solution is washed with ether and concentrated. The residue is recrystallized from isopropanol and ether to yield

5 the title compound (0.63 g, 2.3 mmol) MS m/z: $M^+ = 275$; ^1H NMR (CD_3OD , 300 MHz) δ 9.1 (d, 1H), 8.5 (d, 1H), 8.2-8.3 (m, 2H), 8.0 (d, 1H), 5.2 (s, 2H), 4.1 (s, 2H), 3.7-3.8 (m, 2H), 3.6-3.7 (m, 2H).

EXAMPLE 90. 1-(4-Chlorocinnolin-7-ylmethyl)-piperazin-2-one.

10 4-(t-Butyloxycarbonyl)-piperazin-2-one (0.6 g, 3.0 mmol), EXAMPLE 40, is dissolved in THF (80 mL), cooled in an ice bath and treated with tetrabutylammonium iodide (0.23 g, 0.62 mmol) and 60% sodium hydride (0.12 g, 3.0 mmol). The reaction mixture is stirred at $^{\circ}\text{C}$ for 40 minutes then treated dropwise with a solution of 7-bromomethyl-4-chlorocinnoline (10.7g, 2.7 mmol), Example 15, in THF (20 mL). The resulting solution is warmed to ambient temperature over 2 hours. The solution is evaporated to dryness and the residue is taken up in ethyl acetate and 10 % aqueous sodium bicarbonate solution. The organic layer is separated, washed with water, dried (sodium sulfate) and concentrated. The residue is chromatographed (ethyl acetate) to yield the title compound (0.6 g, 1.6 mmol). A portion of this material (0.21 g, 1.26 mmol) is dissolved in THF (~ 4 mL) and treated with a saturated solution of HCl in ethyl acetate (50 mL) at room temperature for 2 hours. The solution is filtered and concentrated to a residue (0.14 g, 0.4 mmol). MS m/z: $M^+ = 275$; ^1H NMR (CD_3OD , 300 MHz) δ 9.15 (d, 1H), 8.5 (d, 1H), 8.25 (s, 1H), 8.15 (d, 1H), 8.0 (d, 1H), 5.0 (s, 2H), 4.1 (s, 2H), 3.7-3.8 (m, 2H), 3.6-3.7 (m, 2H).

EXAMPLE 91. 1-(4-Chloroquinolin-7-ylmethyl)-3-(S)-methylpiperazin-2-one.

25 4-(Benzylloxycarbonyl)-3-(S)-methylpiperazin-2-one (1.0 g, 4.0 mmol), EXAMPLE 46, is dissolved in THF (60 mL), cooled in an ice bath and treated with tetrabutylammonium iodide (0.10 g, 0.27 mmol) and 60% sodium hydride (0.18 g, 4.4 mmol). The reaction mixture is stirred at 0°C for 30 minutes then treated dropwise with a solution of 7-bromomethyl-4-chloroquinoline (1.12 g, 4.4 mmol), EXAMPLE 14, in THF (5 mL). The resulting solution warmed to room temperature over approximately 1 h then quenched with sodium bicarbonate solution and concentrated. The residue is partitioned between ethyl acetate and water; the organic layer is dried (sodium sulfate) and concentrated. The residue is chromatographed (5 % methanol/methylene chloride) to yield solid 4-(Benzylloxycarbonyl)-1-(4-chloroquinolin-7-ylmethyl)-3-(S)-methyl-piperazin-2-one (1.32 g, 3.1 mmol). A portion of this material (0.10 g, 0.23 mmol) is dissolved in acetonitrile (6 mL) and treated with iodo trimethyl-silane (0.1 mL, 0.75

mmol) at room temperature for 2 hours. The reaction is quenched with methanol and concentrated to dryness. Methanol addition and concentration is repeated six times. The final residue is taken up in 2M aqueous HCl; the solution is washed with ether and concentrated to yield the title compound. MS m/z: M⁺ = 289; ¹H NMR (CD₃OD, 300 MHz) δ 9.2 (d, 1H), 8.6 (d, 1H), 8.2-8.3 (m, 2H), 8.0 (d, 1H), 5.1 (q, 1H), 4.3-4.4 (m, 1H), 3.8-4.0 (m, 2H), 3.6-3.8 (m, 3H), 1.75 (d, 3H).

EXAMPLE 92. 1-[2-(Pyridin-4-ylamino)-ethyl]-piperazin-2-one.

A. 4-(tert-Butyloxycarbonyl)-1-(2-aminoethyl)-piperazin-2-one.

4-(tert-Butyloxycarbonyl)-piperazin-2-one (8.0 g, 40 mmol), EXAMPLE 40, is dissolved in THF (160 mL), cooled in an ice bath and treated with 60 % sodium hydride (1.9 g, 48 mmol). The reaction mixture is stirred 40 minutes, then treated with tetra-butylammonium iodide (0.35 g, 0.95 mmol) and bromoacetonitrile (3.4 mL, 48 mmol). After 2 h the reaction is quenched with water, concentrated to a small volume and extracted with methylene chloride (3 X). The combined organic extracts are concentrated and the residue is chromatographed (50 % ethyl acetate/hexane) to give 4-(tert-butyloxycarbonyl)-1-cyanomethyl-piperazin-2-one (5.2 g, 21.7 mmol). This material is dissolved in ethanol (140 mL) and treated with platinum oxide (0.83 g) at 50 PSI of hydrogen gas for 24 hours. The catalyst is removed by filtration and the solution is concentrated to yield 4-(tert-butyloxycarbonyl)-1-(2-aminoethyl)-piperazin-2-one (5.2 g, 21.6 mmol). ¹H NMR (CDCl₃, 300 MHz) δ 4.08 (s, 2H), 3.62 (m, 2H), 3.44 (t, 2H), 3.38 (t, 2H), 2.89 (t, 2H).

B. 4-(tert-Butyloxycarbonyl)-1-[2-(2,3,5,6-tetrachloropyridin-4-ylamino)-ethyl]-piperazin-2-one.

4-(tert-Butyloxycarbonyl)-1-(2-aminoethyl)-piperazin-2-one (4.0 g, 16 mmol) is dissolved in methylene chloride (150 mL) and treated with 4-nitro-2,3,5,6-tetrachloro-pyridine (4.8 g, 18 mmol) and N-methylmorpholine (4.0 mL, 36 mmol). The reaction mixture is stirred for 5 h, concentrated and the residue is purified by chromatography (50% ethyl acetate/hexane) to give the title compound (4.8 g, 10.5 mmol). Fab MS m/z: 457, 469, 461, [M+1]⁺; ¹H NMR (CDCl₃, 300 MHz) δ 6.00 (t, 1H), 4.10 (s, 2H), 3.97 (m, 2H), 3.66 (m, 2H), 3.38 (m, 2H).

C. 1-[2-(Pyridin-4-ylamino)-ethyl]-piperazin-2-one.

4-(tert-Butyloxycarbonyl)-1-[2-(2,3,5,6-tetrachloropyridin-4-ylamino)-ethyl]-piperazin-2-one (3.5 g, 7.6 mmol) is dissolved in methanol (20 mL) and 0.5 M sodium methoxide in methanol (150 mL, 75 mmol). The solution is treated with Pd/C (0.5 g) and agitated under 50 PSI of hydrogen gas for 16 hours. The solvent is removed and the residue is extracted with methylene chloride which is filtered. The filtrate is concentrated and loaded onto a silica flash column. The column is eluted with 5% MeOH/CH₂Cl₂ followed by NH₄OH/MeOH/CH₂Cl₂ (1:5:95)

and NH₄OH/MeOH/CH₂Cl₂ (1:10:70) to yield 4-(tert-Butyloxycarbonyl)-1-[2-(pyridin-4-ylamino)-ethyl]-piperazin-2-one as a white foam (1.5 g, 4.7 mmol). This material (1.5 g, 4.7 mmol) is treated with 20% trifluoroacetic acid in methylene chloride (110mL) at ambient temperature for 2 hours. The solution is concentrated and the residue is treated with saturated bicarbonate solution and ammonium hydroxide until a basic solution is obtained. The solution is applied to a silica column and eluted with NH₄OH/MeOH/CH₂Cl₂ (1:10:60) and 1-[2-(pyridin-4-ylamino)-ethyl]-piperazin-2-one is isolated as a mixture of desired product and inorganic salts (estimate 25 % by weight) EI MS m/z: 220, M⁺; ¹H NMR (CD₃OD, 300 MHz) δ 8.07 (d, 2H), 6.96 (d, 2H), 3.77 (s, 2H), 3.65 (m, 6H), 3.44 (t, 2H).

10

EXAMPLE 93. 1-[2-((Methyl)-(pyridin-4-yl)-amino)-ethyl]-piperazin-2-one trifluoroacetate.

4-(tert-Butyloxycarbonyl)-1-[2-(2,3,5,6-tetrachloropyridin-4-ylamino)-ethyl]-piperazin-2-one (0.19 g, 0.41 mmol), Example 92, Part B, is dissolved in DMF (3 ml) and treated with 60 % NaH (20 mg, 0.5 mmol). After 10 minutes methyl iodide (0.025 ml, 0.40 mmol) is added and the yellow solution is stirred at r.t. overnight. The solution is diluted with EtOAc and washed with H₂O (6 X). The organic layer is dried (MgSO₄) and concentrated to a residue (0.19 g, 0.40 mmol). The residue is dissolved in methanol (2 ml) and treated with 0.5 M NaOMe in MeOH (8 ml, 4.0 mmol)). The solution is treated with Pd/C and agitated under 60 PSI of hydrogen gas overnight and filtered. The filtrate is concentrated and extracted several times with CH₂Cl₂; removal of solvent in vacuo gives 4-(tert-Butyloxycarbonyl)-1-[2-((methyl)-(pyridin-4-yl)-amino)-ethyl]-piperazin-2-one as an amorphous residue (0.16 g). EI MS m/z: 335, [M+1]⁺; ¹H NMR (CDCl₃, 300 MHz) δ 8.21 (d, 2H), 6.56 (d, 2H), 3.99 (s, 2H), 3.60 (t, 2H), 3.53 (t, 2H), 3.47 (t, 2H), 3.28 (t, 2H), 2.98 (s, 3H), 1.46 (s, 9H). Treatment of the above product with 20% TFA/CH₂Cl₂ (10 mL) at r.t. for 1 h gives, after concentration, the title compound as a residue which is used without further purification. ¹H NMR (CD₃OD, 300 MHz) δ 8.14 (d, 2H), 7.30 (br, 1H), 7.00 (br, 1H), 3.88-3.67 (m, 8H), 3.53 (t, 2H), 2.26 (s, 3H).

EXAMPLE 94. 1-[2-(3-Methylpyridin-4-yl-amino)-ethyl]-piperazin-2-one.

30 A. 4-[2-(3-Methylpyridin-4-ylimino)-ethyl]-3-oxo-piperazine-1-carboxlic acid benzyl ester.

4-(Benzylloxycarbonyl)-piperazin-2-one (4.7 g, 20 mmol) is dissolved in THF (50 mL) and treated with 1.5M LDA (20 mL, 30 mmol) at 0°C. The reaction mixture is treated with condensed ethylene oxide (3 mL, 40 mmol) and stirred at r.t. overnight. The mixture is neutralized with 2N HCl, concentrated, and extracted with EtOAc. The EtOAc layer is washed with H₂O and concentrated to a crude residue. Further extraction of the crude with Et₂O and

concentration of the ethereal layer gives an oil (1.5 g). The above oil is dissolved in CH_2Cl_2 (25 mL) and added to the solution of 2M oxalyl chloride (7.5 mL, 15 mmol) and DMSO (2.3 mL, 29.7 mmol) in CH_2Cl_2 (25 mL) at -60°C. After 15 minutes, Et_3N (2.1 ml, 15 mmol) is added. The mixture is stirred at -50 °C for 10 minutes then warmed to r.t for 10 minutes. The reaction is quenched with 0.5 N HCl and extracted with CH_2Cl_2 . The CH_2Cl_2 layer is washed with 0.5 N HCl, brine (2 X), H_2O , and concentrated to a residue. The residue is purified by chromatography (2% MeOH/ CH_2Cl_2) to give 4-amino-3-methyl pyridine as an oil (0.5 g, 1.6 mmol). A solution of the oil (0.2 g, 2 mmol), and (1R)-(-)-10-camphorsulfonic acid (15 mg) in toluene (100 ml) is refluxed with a Dean Stark set up overnight. The mixture is concentrated and the residue is purified by chromatography (2-4% MeOH/ CH_2Cl_2) to give the title imine as a white foam (0.20 g, 0.54 mmol). Ion spray MS m/z: 367, [M+1]⁺; ¹H NMR (CDCl_3 , 300 MHz) δ 8.20 (d, 1H), 8.14 (s, 1H), 7.35 (s, 5H), 6.60 (d, 1H), 6.18 (dd, 1H), 5.15 (s, 2H), 4.97 (d, 1H), 4.30 (s, 2H), 3.78 (t, 2H), 3.50 (bm, 2H), 2.15 (s, 3H).

B. 1-[2-(3-Methylpyridin-4-yl-amino)-ethyl]-piperazin-2-one.

4-[2-(3-Methylpyridin-4-ylimino)-ethyl]-3-oxo-piperazine-1-carboxlic acid benzyl ester (0.20 g, 0.54 mmol) is dissolved in anhydrous ethanol (20 mL) and hydrogenated at 50 PSI with 10% Pd/C overnight. After filtration, the filtrate is concentrated. The residue is treated with Pd black in 5% $\text{HCO}_2\text{H}/\text{CH}_2\text{Cl}_2$ (10 ml) for 10 minutes. Filtration and concentration gives crude residue, which is purified by chromatography using $\text{NH}_4\text{OH}/\text{MeOH}/\text{CH}_2\text{Cl}_2$ (1:5:95) to give the title compound as a clear syrup (0.078 g, 0.33 mmol). ¹H NMR (CDCl_3 , 300 MHz) δ 8.17 (d, 1H), 8.03 (s, 1H), 7.35 (s, 5H), 6.36 (d, 1H), 5.30 (b, 1H), 3.74 (t, 2H), 3.53 (s, 2H), 3.38 (m, 4H), 3.08 (t, 2H), 2.02 (s, 3H).

EXAMPLE 95. 1-[2-(Pyridazin-4-ylamino)-ethyl]-piperazin-2-one.

1-(2-Aminoethyl)-4-(tert-butyloxycarbonyl)-piperazin-2-one from EXAMPLE 92, Part A (1.0 g, 4.1 mmol) is treated with 3,4,5-trichloropyridazine (0.81 g, 4.1 mmol), triethylamine (0.57 mL, 4.1 mmol), THF (25 mL) and heated to 120°C in a sealed tube for 3 hours. Upon cooling, the solution is diluted with ethyl acetate and washed with aqueous sodium bicarbonate (25 mL), water and dried over sodium sulfate. The organic layer is concentrated and chromatographed (5% methanol/methylene chloride) to give a mixture of isomers (0.8 g, 20 mmol). The mixture is dissolved in 0.5 M sodium methoxide in methanol (200 mL), treated with 10% Pd/C (0.5 g) and agitated under 50 PSI of hydrogen for 20 hours. The reaction mixture is filtered; the filtrate is concentrated to a residue which is chromatographed ($\text{NH}_4\text{OH}/\text{H}_2\text{O}/\text{MeOH}/\text{EtOAc}$, 1:1:2:90) to give crude 4-(tert-butyloxycarbonyl)-1-[2-(pyridazin-4-ylamino)-ethyl]-piperazin-2-one. This material is dissolved in a minimal amount of THF and treated with a saturated solution of HCl in

ethyl acetate (50 mL). The solution is stirred at ambient temperature for 2 h and diluted with diethyl ether (50 mL). The precipitated title compound is collected and air dried (0.5 g, 1.7 mmol). MS m/z: 367, [M+1]⁺; ¹H NMR (CD₃OD, 300 MHz) δ 8.8 (d, 1H), 8.5 (s, 1H), 7.4 (d, 1H), 4.1 (s, 2H), 3.5-3.8 (m, 8H).

5

EXAMPLE 96. 4-[3-(4-tert-Butoxycarbonylamino-pyridin-3-yl)-propenyl]-3-oxo-piperazine-1-carboxylic acid tert-butyl ester and 4-[3-(4-tert-butoxycarbonylamino-pyridin-3-yl)-allyl]-3-oxo-piperazine-1-carboxylic acid tert-butyl ester.

A. 1-Allyl-4-(tert-butyloxycarbonyl)-piperazin-2-one.

10 4-(tert-Butyloxycarbonyl)-piperazin-2-one (1.0 g, 5.0 mmol), EXAMPLE 40, is alkylated with allyl bromide (0.48 ml, 5.5 mmol) in THF (20 ml) using the procedure described in Example 92, Part A. The title compound (0.92 g, 3.8 mmol) is obtained as a colorless liquid after chromatographed (50 % ethyl acetate/hexane). EI MS m/z 240 (M⁺); ¹H NMR (CDCl₃, 300 MHz) δ 5.80-5.68 (m, 1H), 5.23-5.15 (m, 2H), 4.09 (s, 2H), 4.03 (d, 2H), 3.63 (t, 2H), 3.30 (t, 2H), 1.45 (s, 9H).

B. 4-[3-(4-tert-Butoxycarbonylamino-pyridin-3-yl)-propenyl]-3-oxo-piperazine-1-carboxylic acid tert-butyl ester and 4-[3-(4-tert-butoxycarbonylamino-pyridin-3-yl)-allyl]-3-oxo-piperazine-1-carboxylic acid tert-butyl ester

15 1-Allyl-4-(tert-butyloxycarbonyl)-piperazin-2-one (0.49 g, 2.0 mmol) is treated with (3-iodo-pyridin-4-yl)-carbamic acid tert-butyl ester (0.64 g, 2.0 mmol), Pd(OAc)₂ (14 mg, 0.06 mmol), P(o-tol)₃ (37 mg, 0.12 mmol), and Et₃N (0.56 mmol) in a seal tube. The mixture is stirred at 100 °C overnight, then diluted with CH₂Cl₂ and washed H₂O (2 X). The CH₂Cl₂ layer is concentrated and the residue is chromatographed (5% MeOH/CH₂Cl₂) to give a mixture of two isomers (0.40 g, 0.92 mmol). The mixture is separated into its constituent isomers upon further chromatography (EtOAc) to give 4-[3-(4-tert-butoxycarbonylamino-pyridin-3-yl)-propenyl]-3-oxo-piperazine-1-carboxylic acid tert-butyl ester (90 mg, 0.21 mmol, higher R_f value) and 4-[3-(4-tert-butoxycarbonylamino-pyridin-3-yl)-allyl]-3-oxo-piperazine-1-carboxylic acid tert-butyl ester (0.24 g, 0.56 mmol, lower R_f value). For the former: MS m/z 433 (M+1); ¹H NMR (CDCl₃, 300 MHz) δ 8.38 (d, 1H), 8.28 (s, 1H), 7.93 (d, 1H), 7.48 (d, 1H), 6.67 (s, 1H), 5.10 (m, 1H), 4.15 (s, 2H), 3.70 (t, 2H), 3.46 (t, 2H), 3.39 (d, 2H), 1.48 (s, 9H), 1.45 (s, 9H). For the latter: MS m/z 433 (M+1); ¹H NMR (CDCl₃, 300 MHz) δ 8.39 (s, 1H), 8.37 (d, 1H), 7.98 (d, 1H), 6.77 (s, 1H), 6.52 (d, 1H), 6.07 (m, 1H), 4.23 (d, 2H), 4.12 (s, 2H), 3.69 (t, 2H), 3.40 (t, 2H), 1.52 (s, 9H), 1.45 (s, 9H).

EXAMPLE 97. 4-[3-(4-tert-Butoxycarbonylamino-pyridin-3-yl)-propyl]-3-oxo-piperazine-1-carboxylic acid tert-butyl ester

A mixture of the two isomers from EXAMPLE 96, Part B. (0.11 g, 0.25 mmol) is dissolved in MeOH (7 ml), treated with 10% Pd/C and is stirred under a balloon of hydrogen for 4 hours. Filtration and concentration gives a white foam (80 mg, 0.18 mmol). EI MS m/z 434 (M+); ¹H NMR (CDCl₃, 300 MHz) δ 8.33 (d, 1H), 8.30 (s, 1H), 8.05 (d, 1H), 4.08 (s, 2H), 3.64 (t, 2H), 3.50 (t, 2H), 3.35 (t, 2H), 2.58 (t, 2H), 1.90 (m, 2H), 1.57 (s, 9H), 1.48 (s, 9H).

EXAMPLE 98. 4-(Benzylloxycarbonyl)-1-(2-pyrrolo[3,2-c]pyridin-1-ylethyl)-piperazin-2-one

4-(Benzylloxycarbonyl)-1-(2-hydroxyethyl)-piperazin-2-one, prepared as described in EXAMPLE 94, part A. (0.26 g, 0.94 mmol) in methylene chloride (6 mL) is treated with triphenyl phosphine (0.60 g, 2.3 mmol), imidazole (0.16 g, 2.3 mmol), and iodine (0.47 g, 1.9 mmol) for 0.5 h at 0 °C. The reactin mixture is partitioned between water and methylene chloride; the organic layer is concentrated and the residue is chromatographed (15 % EtOAc/ methylene chloride) to give 4-(benzylloxycarbonyl)-1-(2-iodoethyl)-piperazin-2-one (0.24 g, 0.62 mmol). Pyrrolo[3,2-c]pyridine (0.073 g, 0.62 mmol) is dissolved in DMF (3 mL) and treated with 60 % sodium hydride (0.03 g, 0.74 mmol) and all of the 4-(benzylloxycarbonyl)-1-(2-iodoethyl)-piperazin-2-one from the previous step; the reaction mixture is stirred at r.t. for 16 g. The reaction mixture is concentrated to dryness and the residue is partitioned between water and methylene chloride. The organic layer is concentrated and subjected to chromatography (2-5 % MeOH/methylene chloride) to yield the title compound (0.028 g, 0.074 mmol) Ion Spray MS m/z: 379, [M+1]⁺.

EXAMPLE 99. (±)-1-(3-Amino-4-cyano-benzyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid methyl ester.

A. (±)-1-[3-(Benzhydrylidene-amino)-4-cyano-benzyl]-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid methyl ester

A solution containing (±)-1-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-6-oxo-piperazine-2-carboxylic acid methyl ester (55 mg, 0.12 mmol) in CH₂Cl₂ (1 mL) is cooled to 0°C. DIPEA (24 mg, 0.18 mmol) is then added followed by the addition of 6-chloro-benzo[b]thiophene-2-sulfonyl chloride (32 mg, 0.12 mmol), EXAMPLE 1. The reaction mixture is warmed to ambient temperature. After 16 h, the reaction mixture is absorbed directly onto silica gel and chromatographed (CH₂Cl₂ to 2% MeOH/ CH₂Cl₂) to provide 60 mg (73%) of the title compound. ¹H NMR (300 MHz, CDCl₃) δ 2.77 (dd, J = 12.3, 3.4 Hz, 1H), 3.50-3.72 (m, 3H), 3.79 (s, 3H), 4.15 (dd, J = 12.3, 1.4 Hz, 1H), 4.24 (d, J = 16.9 Hz, 1H), 5.41 (d, J = 15.3 Hz,

1H), 6.50 (s, 1H), 6.76 (dd, $J = 7.9, 1.4$ Hz, 1H), 7.11-7.86 (m, 15H) ppm; MS (ISP loop): m/z 683 (M+H).

B. (±)-1-(3-Amino-4-cyano-benzyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid methyl ester

5 Concentrated HCl (12M, one drop) is added at 0°C to a mixture containing (±)-1-[3-(benzhydrylidene-amino)-4-cyano-benzyl]-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid methyl ester (60 mg, 0.08 mmol) in MeOH (5 mL). Added THF (2 mL) followed by a second drop of 12M HCl and warmed reaction mixture to ambient temperature. The reaction is quenched by pouring the reaction mixture onto a 1:1 mixture of

10 CH_2Cl_2 /aqueous NaHCO_3 and the layers are separated. The aqueous phase is washed with CH_2Cl_2 and then the combined organic phase is washed with brine, dried over anhydrous MgSO_4 , filtered and concentrated. The crude residue is chromatographed on silica gel (CH_2Cl_2 to 4% MeOH/ CH_2Cl_2) to provide 42 mg (93%) of the title compound. ^1H NMR (300 MHz, CDCl_3) δ 2.98 (dd, $J = 12.5, 3.5$ Hz, 1H), 3.60 (d, $J = 16.8$ Hz, 1H), 3.69 (d, $J = 15.3$ Hz, 1H), 3.79 (s, 3H), 3.98 (m, 1H), 4.21-4.31 (m, 2H), 4.44 (br s, 2H), 5.36 (d, $J = 15.3$ Hz, 1H), 6.47 (dd, $J = 8.0, 1.4$ Hz, 1H), 6.54 (s, 1H), 7.26 (d, $J = 8.0$ Hz, 1H), 7.45 (dd, $J = 8.5, 1.8$ Hz, 1H), 7.80-7.86 (m, 3H) ppm; MS (ISP loop): m/z 519 (M+H).

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EXAMPLE 100. (±)-1-(3-Amino-4-cyano-benzyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid.

Water (5 drops) is added to a solution containing (±)-1-(3-amino-4-cyano-benzyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid methyl ester (30 mg, 0.05 mmol), EXAMPLE 99, in a 1:1 mixture of THF/MeOH (2 mL). At ambient temperature, LiOH monohydrate (7 mg, 1.66 mmol) is then added. After 16 h, the reaction mixture is diluted with water and purified by reverse-phase HPLC [Buffer A: water w/ 0.1% TFA; Buffer B: CH_3CN w/ 0.1% TFA; Gradient: 0% B to 60% B over 30 min] to provide 10 mg (34%) of the title compound as a white solid. ^1H NMR (300 MHz, $d_6\text{-DMSO}$) δ 3.18 (dd, $J = 12.1, 3.5$ Hz, 1H), 3.61 (d, $J = 16.0$ Hz, 1H), 3.77 (d, $J = 16.0$ Hz, 1H), 3.95 (d, $J = 16.0$ Hz, 1H), 4.06 (d, $J = 12.1$ Hz, 1H), 4.14 (m, 1H), 6.40 (d, $J = 8.0$ Hz, 1H), 6.54 (s, 1H), 7.21 (d, $J = 8.0$ Hz, 1H), 7.57 (dd, $J = 8.6, 1.9$ Hz, 1H), 8.06 (d, $J = 8.6$ Hz, 1H), 8.18 (s, 1H), 8.33 (s, 1H) ppm; MS (ISP loop): m/z 505 (M+H).

EXAMPLE 101. 4-[4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-2-oxo-piperazine-1-ylmethyl]benzamidine.

To a solution of 4-(2-oxopiperazin-1-ylmethyl)benzamidine bistrifluoroacetate (0.38 g, 0.83mmol), EXAMPLE 66, in CH_2Cl_2 (5 mL) is added Et_3N (0.35 mL, 2.6 mmol) and 6-chloro-benzo[b]thiophene-2-sulfonyl chloride (0.23 g, 0.85 mmol, EXAMPLE 1. After 6 hours, the solution is concentrated. The product is purified by RP-HPLC eluting in a gradient of 10% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (0.1% TFA) to 70% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (0.1% TFA). The appropriate collected fractions are lyophilized to afford the title compound as a white solid (0.37 g, 0.65 mmol). ^1H NMR (d^6 -DMSO, 300MHz) δ 9.33 (bs, 2H), 8.96 (bs, 2H), 8.30 (s, 1H), 8.18 (s, 1H), 8.04 (d, 1H), 7.70 (m, 2H), 7.50 (m, 1H), 7.28 (m, 2H), 4.55 (s, 2H), 3.86 (s, 2H), 3.44 (m, 2H), 3.22 (m, 2H).

10 The following compounds are prepared from 1-(4-Aminoquinazoline-7-ylmethyl)-3-ethyl-piperazine-2-one, Example 77, and the appropriate sulfonyl chloride using the method of Example 101.

Example	Name	m/z (M+H)
102	4-[4-(4-Methoxy-benzenesulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine	403
103	4-[4-(5-Chloro-thieno[3,2-b]pyridine-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine	463, 465
104	4-[4-(6-Chloro-thieno[2,3-b]pyridine-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine	464, 466 Cl pattern
105	4-[2-Oxo-4-(thieno[2,3-c]pyridine-2-sulfonyl)-piperazin-1-ylmethyl]-benzamidine	430
106	4-[4-(7-Chloro-thieno[2,3-c]pyridine-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine	464, 466 Cl pattern
107	4-[4-(5'-Chloro-[2,2']bithiophenyl-5-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine	495, 497 Cl pattern
108	4-[4-(4-Chloro-thieno[3,2-c]pyridine-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine	464, 466 Cl pattern
109	4-[2-Oxo-4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-benzamidine	387
110	4-[4-(Benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine	429
111	4-Amino-3-[4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine	478, 480 Cl pattern
112	3-[2-Oxo-4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-benzamidine	387
113	3-[4-(6-Fluoro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-	447

	ylmethyl]-benzamidine	
114	3-[4-(4-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine	463, 465 Cl pattern
115	3-[4-(5-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine	463, 465 Cl pattern
116	3-[4-(6-Methoxy-naphthalene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine	453
117	3-{4-[5-(5-Nitro-pyridine-2-sulfonyl)-thiophene-2-sulfonyl]-2-oxo-piperazin-1-ylmethyl}-benzamidine	565
118	3-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine	463, 465 Cl pattern
119	3-{4-[2-(3-Chloro-phenyl)-ethenesulfonyl]-2-oxo-piperazin-1-ylmethyl}-benzamidine	433, 435 Cl pattern
120	3-[2-Oxo-4-(4-phenylazo-benzenesulfonyl)-piperazin-1-ylmethyl]-benzamidine	477
121	3-[4-(Benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine	429

EXAMPLE 122. 4-[4-(6-Chloro-1H-benzoimidazol-2-ylmethyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine.

Hydrogen chloride gas is bubbled into an ice-cooled solution of 4-[4-(6-chloro-1H-benzoimidazol-2-ylmethyl)-2-oxo-piperazin-1-ylmethyl]-benzonitrile (100 mg, 0.264 mmol),

5 (prepared by deprotecting 4-(4-cyanobenzyl)-3-oxopiperazine-1-carboxylic acid benzyl ester, EXAMPLE 66, Part A, followed by alkylation with 6-chloro-2-chloromethylbenzimidazole) in 15 mL of methanol. The solution contained 3Å molecular sieves. The reaction mixture is stored at -30°C. The methanol is removed on the rotovap. Fresh methanol (20 ml) is added followed by a stream of ammonia gas. The resulting mixture is heated to reflux for three hours. The

10 reaction mixture is filtered at room temperature. The mother liquor is condensed and the resulting residue is purified by reverse phase HPLC (0-50 % ACN/H₂O). The product is isolated as a white solid with a melting point of 91-95°C .

MS C₂₀H₂₁CIN₆O m/z: 397, 399. Anal. cald. for C₂₀H₂₁CIN₆O•3C₂HF₃O₂: C, 42.26; H, 3.27; N, 11.37. Found C, 42.20; H, 3.44; N, 11.36.

15

EXAMPLE 123. 4-[4-[3-(5-Chloro-thiophen-2-yl)-(E)-acryloyl]-2-oxopiperazin-1-ylmethyl]benzamidine.

To a solution of 4-(2-oxopiperazin-1-ylmethyl)benzamidine bistrifluoroacetate (75 mg, 0.16 mmol), EXAMPLE 66, in 1.5 mL of DMF is added N,N-diisopropylethylamine (0.14 mL, 0.80 mmol). After stirring 10 min at room temperature, 3-(5-chloro-thiophen-2-yl)-(E)-acrylic acid (32 mg, 0.17 mmol), EXAMPLE 25, is added, followed by 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) (55 mg, 0.17 mmol). The resulting mixture is stirred at room temperature for 16 h and the solution is concentrated. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 70% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are combined and lyophilized to provide the title compound (77 mg, 0.15 mmol) as a white solid.

10 ¹H NMR (d₆-DMSO, 300 MHz) δ 9.27 (bs, 2H), 9.10 (bs, 2H), 7.77 (d, 2H), 7.65 (d, 1H), 7.49 (dd, 2H), 7.39 (m, 1H), 7.15 (d, 1H), 6.89 (d, 1H), 4.65 (s, 2H), 4.45, 4.21 (m, 2H, rotamers), 3.80 (m, 2H), 3.35 (m, 2H). ESI MS, [M+H]⁺=403,405 (Cl pattern).

EXAMPLE 124. 3-[4-[3-(5-Chloro-thiophen-2-yl)-(E)-acryloyl]-2-oxopiperazin-1-ylmethyl]benzamidine.

15 The title compound is prepared as described in EXAMPLE 123 using 3-(5-chlorothiophen-2-yl)-(E)-acrylic acid (EXAMPLE 25) and 3-(2-oxopiperazin-1-ylmethyl)benzamidine bistrifluoroacetate (prepared from 3-bromomethyl toluyl nitrile as described in EXAMPLE 66). ¹H NMR (DMSO-d₆, 300 MHz) δ 9.32 (bs, 2H), 9.16 (bs, 2H), 7.65 (m, 5H), 7.39 (m, 1H), 7.15 (d, 1H), 6.89 (d, 1H), 4.64 (s, 2H), 4.44, 4.21 (m, 2H, rotamers), 3.93, 3.79 (m, 2H, rotamers), 3.36 (m, 2H). ESI MS, [M+H]⁺=403,405 (Cl pattern).

EXAMPLE 125. 3-[4-(6-Chloro-1H-benzoimidazol-2-ylmethyl)-2-oxo-piperazin-1-ylmethyl]benzamidine.

25 A white solid (13.0 mg, 13%). C₂₀H₂₁ClN₆O MS m/z: 397, 399 Anal. cald. for C₂₀H₂₁ClN₆O · 3C₂HF₃O₂: C, 42.26; H, 3.27; N, 11.37. Found C, 43.70; H, 3.71; N, 11.95.

EXAMPLE 126. 1-(2-Aminoquinolin-6-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-sulfonyl)piperazin-2-one.

30 The title compound is prepared as described in Example 101 using 1-(2-aminoquinolin-6-ylmethyl)piperazin-2-one, EXAMPLE 67, and 5'-chloro-[2,2']bithiophenyl-5-sulfonyl chloride, EXAMPLE 2. The crude product is triturated in CH₂Cl₂ and filtered to provide the title compound as a white solid. ¹H NMR (d₆-DMSO, 300 MHz) δ 7.82 (d, 1H), 7.68 (d, 1H), 7.42 (m, 3H), 7.36 (d, 1H), 7.25 (d, 1H), 7.20 (d, 1H), 6.70 (d, 1H), 6.43 (bs, 2H), 4.53 (s, 2H), 3.78 (s, 2H), 3.31 (m, 4H). MS (ion spray) m/z 519, 521, (M+H), Cl pattern.

EXAMPLE 127. 6-[4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazin-1-ylmethyl]-1H-quinolin-2-one.

The title compound is prepared as described in EXAMPLE 101, using 6-(2-oxopiperazin-1-ylmethyl)-1H-quinolin-2-one, minor product from EXAMPLE 67, Part D, and

5 6-chlorobenzo[b]thiophene-2-sulfonyl chloride, EXAMPLE 1. The crude product is triturated in CH_2Cl_2 and filtered to provide the title compound as a white solid. ^1H NMR (d_6 -DMSO, 300 MHz) δ 11.72 (bs, 1H), 8.33 (s, 1H), 8.18 (s, 1H), 8.07 (d, 1H), 7.78 (d, 1H), 7.58 (dd, 1H), 7.45 (s, 1H), 7.30 (dd, 1H), 7.18 (d, 1H), 6.46 (d, 1H), 4.52 (s, 2H), 3.86 (s, 2H), 3.43 (m, 2H), 3.31 (m, 2H). MS (ion spray) m/z 488, 490, (M+H), Cl pattern.

10

The following compounds are prepared using starting materials prepared as described in Examples 67, 68 and 73 and the appropriate carboxylic acid according to the method of Example 123.

Example	Name	m/z (M+H)
128	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-thieno[2,3-c]pyridin-3-ylmethyl-piperazin-2-one	478, 480 Cl pattern
129	1-(2-Amino-quinoxalin-6-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one	
130	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-thieno[2,3-c]pyridin-2-ylmethyl-piperazin-2-one	478, 480 Cl pattern
131	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-thieno[3,2-c]pyridin-2-ylmethyl-piperazin-2-one	478, 480 Cl pattern
132	1-(2-Amino-quinolin-6-ylmethyl)-4-(6-chloro-thieno[2,3-b]pyridine-2-sulfonyl)-piperazin-2-one	488, 490 Cl pattern
133	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(1-hydroxy-isoquinolin-6-ylmethyl)-piperazin-2-one	488, 490 Cl pattern
134	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(1-chloro-isoquinolin-6-ylmethyl)-piperazin-2-one	506, 508 Cl pattern
135	7-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-2H-isoquinolin-1-one	488, 490 Cl pattern
136	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(1-chloro-isoquinolin-7-ylmethyl)-piperazin-2-one	506, 508 Cl pattern
137	1-(7-Amino-thieno[2,3-c]pyridin-2-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one	493, 495 Cl pattern

138	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(2-chloro-quinolin-6-ylmethyl)-piperazin-2-one	506, 508 CI pattern
139	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-quinolin-6-ylmethyl-piperazin-2-one	472, 474 CI pattern
140	7-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-1H-quinolin-2-one	488, 490 CI pattern
141	1-(2-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one	487, 489 CI pattern
142	1-(4-Amino-thieno[3,2-c]pyridin-2-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one	493, 495 CI pattern
143	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(1,2,3,4-tetrahydro-isoquinolin-6-ylmethyl)-piperazin-2-one	475, 477 CI pattern
144	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-isoquinolin-6-ylmethyl-piperazin-2-one	472, 474 CI pattern
145	1-(2-Amino-quinolin-6-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one	487, 489 CI pattern
146	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(decahydro-isoquinolin-6-ylmethyl)-piperazin-2-one	482, 484 CI pattern
147	1-(1-Amino-isoquinolin-6-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one	487, 489 CI pattern
148	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(decahydro-isoquinolin-7-ylmethyl)-piperazin-2-one	482, 484 CI pattern
149	1-(1-Amino-isoquinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one	487, 489 CI pattern
150	1-(4-Amino-thieno[3,2-c]pyridin-3-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one	493, 495 CI pattern
151	(+/-)-[1-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-3-oxo-4-thieno[3,2-c]pyridin-2-ylmethyl-piperazin-2-yl]-acetic acid	536, 538 CI pattern
152	(+/-)-[1-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-3-oxo-4-thieno[2,3-c]pyridin-2-ylmethyl-piperazin-2-yl]-acetic acid	536, 538 CI pattern
153	1-(1-Amino-isoquinolin-6-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-(E)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one	471, 473 CI pattern
154	1-(1-Amino-isoquinolin-6-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	475, 477 CI pattern

155	(3S)-1-(7-Chloro-isoquinolin-3-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-methoxymethyl-piperazin-2-one	494, 496, 498, Cl ₂ pattern
156	(3S)-1-(7-Chloro-isoquinolin-3-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-(E)-acryloyl]-3-methoxymethyl-piperazin-2-one	490, 492, 494, Cl ₂ pattern
157	(S)-4-[3-(5-Chloro-thiophen-2-yl)-acryloyl]-3-ethyl-1-(4-hydroxy-quinolin-7-ylmethyl)-piperazin-2-one	456, 458 Cl pattern
158	1-(2-Amino-quinolin-6-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-(E)-acryloyl]-piperazin-2-one	427, 429 Cl pattern

The following compounds are prepared from starting materials prepared as described in Example 67 and the appropriate aryl-methyl bromide or allyl-methyl bromide using a K₂CO₃-mediated alkylation reaction.

Example	Name	m/z (M+H)
159	1-(2-Aminoquinolin-6-ylmethyl)-4-(4-methoxybenzyl)piperazin-2-one	377
160	1-(2-Aminoquinolin-6-ylmethyl)-4-6-chlorobenzo[b]thiophen-2-ylmethyl)piperazin-2-one	436, 438 Cl pattern
161	1-(2-Aminoquinolin-6-ylmethyl)-4-(5-methoxy-1H-benzimidazol-2-ylmethyl)piperazin-2-one	417
162	1-(2-Aminoquinolin-6-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-ylmethyl)piperazin-2-one	469, 471 Cl pattern
163	1-(2-Aminoquinolin-6-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-piperazin-2-one	413, 415 Cl pattern
164	1-(2-Aminoquinolin-6-ylmethyl)-4-[3-(3,5-dibromo-4-methoxy-phenyl)-[1,2,4]oxadiazol-5-ylmethyl)piperazin-2-one	601, 603, 605 Br ₂ pattern
165	3-[4-(2-Aminoquinolin-6-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-7-fluoro-1H-quinolin-2-one	431
166	1-(2-Aminoquinolin-6-ylmethyl)-4-(6-chloro-naphthalen-2-ylmethyl)-piperazin-2-one	430

The following compounds are prepared from starting materials prepared as described in

5 Examples 66, 67, 68 and 73 and the appropriate aryl-methyl bromide or allyl-methyl bromide using a K₂CO₃-mediated alkylation reaction.

Example	Name	m/z (M+H)

167	3-(4-Biphenyl-3-ylmethyl-3-oxo-piperazin-1-ylmethyl)-benzamidine	399
168	4-(5-Chloro-1H-indol-2-ylmethyl)-1-(4-chloro-quinolin-7-ylmethyl)-piperazin-2-one	439, 441 Cl pattern
169	1,4-Bis-(5-chloro-1H-indol-2-ylmethyl)-piperazin-2-one	427
170	1-(4-Amino-thieno[3,2-d]pyrimidin-6-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-piperazin-2-one	439, 441 Cl pattern
171	1-(4-Amino-thieno[3,2-d]pyrimidin-6-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	444, 446 Cl pattern
172	1-(4-Amino-thieno[3,2-d]pyrimidin-6-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-piperazin-2-one	420, 422 Cl pattern
173	1-(3-Amino-1H-indazol-6-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-piperazin-2-one	401
174	1-(3-Amino-1H-indazol-6-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	426
175	1-(4-Amino-thieno[2,3-d]pyrimidin-6-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	443
176	4-[4-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-2-oxo-piperazin-1-ylmethyl]-benzamidine	413, 415 Cl pattern
177	4-[4-(6-Chloro-benzo[b]thiophen-2-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-benzamidine	413, 415 Cl pattern
178	4-(4-Cyclohexylmethyl-2-oxo-piperazin-1-ylmethyl)-benzamidine	329
179	1-(1-Amino-isoquinolin-6-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	437, 439 Cl pattern
180	1-(1-Amino-isoquinolin-6-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-(S)-methoxymethyl-piperazin-2-one	457, 459 Cl pattern
181	4-[3-(5-Chloro-thiophen-2-yl)-allyl]-1-[4-(6-methoxy-pyridin-3-yl)-benzyl]-3-(S)-methyl-piperazin-2-one	468
182	4-[3-(5-Chloro-thiophen-2-yl)-allyl]-3-(S)-methyl-1-[4-(6-oxo-1,6-dihydro-pyridin-3-yl)-benzyl]-piperazin-2-one	454
183	(S)-4-(5-Chloro-1H-indol-2-ylmethyl)-1-(4-chloro-quinolin-7-ylmethyl)-3-methoxymethyl-piperazin-2-one	483
184	(S)-4-(5-Chloro-1H-indol-2-ylmethyl)-1-(4-chloro-quinolin-7-ylmethyl)-3-methyl-piperazin-2-one	453

EXAMPLE 185. 1-(4-Aminoquinazolin-7-ylmethyl)-4-(6-chlorobenzo[b]thiophene-2-sulfonyl)piperazin-2-one.

The title compound is prepared as described in EXAMPLE 101, substituting 1-(4-aminoquinazoline-7-ylmethyl)piperazine-2-one bishydrochloride, EXAMPLE 72, for 4-(2-oxopiperazin-1-ylmethyl)-benzamidine. The product is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 70% CH₃CN/H₂O (0.1% TFA). The appropriate collected fractions are lyophilized to afford the title compound as a white solid. MS (ion spray) m/z 488, 490, (M+H). ¹H NMR (d₆-DMSO, 300 MHz) δ 9.65 (s, 2H), 8.80 (s, 1H), 8.30 (m, 2H), 8.20 (s, 1H), 8.05 (d, 1H), 7.60 (m, 3H), 4.70 (s, 2H), 3.85 (s, 2H), 3.50-3.20 (m, 4H).

10

EXAMPLE 186. 4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-sulfonic acid 3-chlorobenzylamide.

To a solution of 1-(4-aminoquinazoline-7-ylmethyl)piperazine-2-one bishydrochloride, EXAMPLE 72, (0.10g, 0.30mmol) is 9 mL of DMF is added 3-chlorobenzyl sulfamyl catechol (0.09g, 0.30mmol), EXAMPLE 4, Et₃N (0.08g, 0.75 mmol) and DMAP (0.001 g, 0.12 mmol). The solution is heated to 60°C. After 16 h, the solution is concentrated. The crude product is purified by RP-HPLC eluting with a gradient of 10% CH₃CN/H₂O (0.1%TFA) to 100% CH₃CN. The product fractions are lyophilized to give the title compound (0.077g, 0.17 mmol) as the TFA salt. ¹H NMR (d₆-DMSO, 300 MHz) δ 9.82 (bs, 2H), 8.98 (s, 1H), 8.52 (d, 1H), 8.32 (d, 1H), 7.60 (m, 2H), 7.35 (m, 4H), 4.69 (AB, 2H), 4.11 (m, 2H), 3.77 (s, 2H), 3.38 (m, 2H), 3.27 (m, 2H). MS (ion spray) m/z 461, 463, (M+H), Cl pattern.

The following compounds are prepared from the compound of Example 72 and the appropriate sulfonyl choride using the method of Example 101.

Example	Name	m/z (M+H)
187	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-thieno[2,3-b]pyridine-2-sulfonyl)-piperazin-2-one	489, 491 Cl pattern
188	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-sulfonyl)-piperazin-2-one	520, 522 Cl pattern
189	4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-sulfonic acid 4-chloro-benzylamide	460
190	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-isoxazol-3-yl-thiophene-2-sulfonyl)-piperazin-2-one	471
191	1-(4-Amino-quinazolin-7-ylmethyl)-4-(thieno[3,2-b]pyridine-2-	455

	sulfonyl)-piperazin-2-one	
192	4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-sulfonic acid [2-(3-chloro-phenyl)-ethyl]-amide	474
193	4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-sulfonic acid [2-(4-chloro-phenyl)-ethyl]-amide	474
194	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-sulfonyl)-piperazin-2-one	472
195	1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-piperazin-2-one	464, 466 Cl pattern
196	4-(3-Amino-benzenesulfonyl)-1-(4-amino-quinazolin-7-ylmethyl)-piperazin-2-one	413

The following compounds are prepared from starting materials obtained as described in Examples 75-88 and the appropriate sulfonyl chloride using the method of Example 101.

Example	Name	m/z (M+H)
197	1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-3-(S)-ethyl-piperazin-2-one	492, 494 Cl pattern
198	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-3-(S)-ethyl-piperazin-2-one	516, 518 Cl pattern
199	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-sulfonyl)-3-(S)-ethyl-piperazin-2-one	548, 550 Cl pattern
200	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-sulfonyl)-3-(S)-methyl-piperazin-2-one	534, 536 Cl pattern
201	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-3-(S)-methyl-piperazin-2-one	502, 504 Cl pattern
202	(+/-)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-methyl-piperazin-2-one	502, 504 Cl pattern
203	(+/-)-[4-(4-Amino-quinazolin-7-ylmethyl)-1-(6-chloro-benzo[b]thiophene-2-sulfonyl)-3-oxo-piperazin-2-yl]-acetic acid	546, 548 Cl pattern

The following compounds are prepared from starting materials obtained as described in

Examples 72 and 73 and the appropriate sulfonyl chloride according to the method of Example 101 or the appropriate carboxylic acid according to the method of Example 123.

Example	Name	m/z (M+H)
204	1-(4-Amino-thieno[3,2-d]pyrimidin-6-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-piperazin-2-one	470, 472 Cl pattern

205	1-(4-Amino-thieno[3,2-d]pyrimidin-6-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one	493, 495 Cl pattern
206	1-(4-Amino-thieno[2,3-d]pyrimidin-6-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one	494, 496 Cl pattern
207	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4-hydroxy-quinazolin-6-ylmethyl)-piperazin-2-one	489, 491 Cl pattern
208	1-(4-Amino-thieno[3,2-d]pyrimidin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one	494, 496 Cl pattern
209	1-(4-Amino-quinazolin-6-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one	488, 490 Cl pattern
210	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(4-hydroxy-quinazolin-7-ylmethyl)-piperazin-2-one	489, 491 Cl pattern
211	1-(4-Amino-thieno[3,2-d]pyrimidin-6-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-piperazin-2-one	478, 480 Br pattern
212	1-(4-Amino-thieno[3,2-d]pyrimidin-6-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-piperazin-2-one	434, 436 Cl pattern

EXAMPLE 213. 4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one.

5 A. 2-[4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-2-oxopiperazin-1-ylmethyl]pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester.

To a solution of 2-(2-oxopiperazin-1-ylmethyl)pyrrolo[3,2-c]pyridin-1-carboxylic acid tert-butyl ester (0.71 g, 2.1 mmol), EXAMPLE 69, in CH₃CN (7 mL) is added triethylamine (0.60 mL, 4.3 mmol) followed by 2-(5-chloro-thiophen-2-yl)-ethenesulfonyl chloride, EXAMPLE 3, (0.57 g,

10 2.1 mmol). The mixture is stirred overnight, then concentrated to dryness. The residue is diluted with CH₂Cl₂ and washed with saturated sodium bicarbonate and brine. The organic layer is dried over MgSO₄, filtered and concentrated in vacuo to give the title compound (1.2 g, 2.1 mmol) as a light yellow solid. The crude material can be used in the subsequent step without further purification. ¹H NMR (CDCl₃, 300 MHz) δ 8.80 (s, 1H), 8.42 (d, 1H), 7.88 (d, 1H), 7.55 (d, 1H), 7.14 (d, 1H), 6.98 (d, 1H), 6.41 (s, 1H), 6.36 (d, 1H), 5.00 (s, 2H), 3.98 (s, 2H), 3.61 (m, 4H), 1.71 (s, 9H). Ion spray MS, [M+H]⁺ = 537, 539, Cl pattern.

15 B. 4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one.

Trifluoroacetic acid (2.2 mL, 28.6 mmol) is added dropwise to a slurry of 2-[4-(6-chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazin-1-ylmethyl]pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (1.32 g, 2.4 mmol) in CH_2Cl_2 (25 mL) at 0°C. After 1.5 hours, the ice bath is removed and the solution stirred at room temperature for 4 hours. The reaction 5 mixture is diluted with methylene chloride and washed with saturated sodium bicarbonate and brine. The organic layer is dried over MgSO_4 , filtered and concentrated in vacuo to give the title compound as the free base. The crude product is purified by RP-HPLC eluting in a gradient of 10% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (0.1% TFA) to 100% CH_3CN and the appropriate product fractions are lyophilized to provide the title compound (1.29 g, 2.2 mmol) as a white solid. ^1H NMR (CDCl_3 , 10 300 MHz) δ 14.90 (bs, 1H), 12.81 (s, 2H), 9.12 (s, 1H), 8.41 (d, 1H), 7.89 (d, 1H), 7.60 (d, 1H), 7.50 (d, 1H), 7.20 (d, 1H), 7.12 (d, 1H), 6.95 (s, 1H), 4.80 (s, 2H), 3.98 (s, 2H), 3.48 (s, 4H). Ion spray MS, $[\text{M}+\text{H}]^+=$ 437, 439, Cl pattern.

EXAMPLE 214. 4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one.

A. 2-[4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazin-1-ylmethyl]pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester.

^1H NMR (CDCl_3 , 300 MHz) δ 8.7 (s, 1H), 8.41 (d, 1H), 7.9-7.8 (m, 3H), 7.45 (d, 1H), 7.25 (d, 1H), 6.31 (s, 1H), 4.95 (s, 2H), 3.98 (s, 2H), 3.65 (m, 2H), 3.55 (m, 2H), 1.68 (s, 9H). Ion spray MS, $[\text{M}+\text{H}]^+=$ 561, 563, Cl pattern.

B. 4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one trifluoroacetate.

^1H NMR ($d_6\text{-DMSO}$, 300 MHz) δ 14.68 (bs, 1H), 12.6 (s, 1H), 9.1 (s, 1H), 8.36 (d, 1H), 8.29 (d, 1H), 8.17 (s, 1H), 8.05 (d, 1H), 7.82 (d, 1H), 7.56 (m, 2H), 6.83 (s, 1H), 4.1 (s, 2H), 3.84 (s, 2H), 3.38 (m, 4H). Ion spray MS, $[\text{M}+\text{H}]^+=$ 461, 463, Cl pattern.

EXAMPLE 215. 4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-1-(5-oxy-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one.

4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one (0.06 g, 0.13 mmol) is dissolved in anhydrous methylene chloride (20 ml), treated with m-chloroperbenzoic acid (0.03 g, mmol) and stirred at room temperature for 4 hours. The solution is diluted with methylene chloride, washed with NaHCO_3 , dried (Na_2SO_4) and concentrated. The residue is purified by flash chromatography (5-10 % $\text{MeOH}/\text{CH}_2\text{Cl}_2$) and converted to the TFA salt to provide the title compound (0.015 g, 0.032 mmol). ^1H NMR (CDCl_3 , 300 MHz) δ 9.14 (bs, 1H), 8.95 (d, 1H), 7.8-7.87 (m, 3H), 7.57 (d, 1H), 7.48 (dd, 1H),

6.87 (s, 1H), 4.90 (s, 2H), 3.95 (s, 2H), 3.86 (s, 3H), 3.49 (s, 3H). EI MS, $[M^+]$ = 474, 476, Cl pattern.

EXAMPLE 216. 4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-1-(1-methyl-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one.

4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one (0.59 g, 1.28 mmol), EXAMPLE 214, is dissolved in anhydrous DMF (30 ml), cooled in an ice bath, treated with 60 % sodium hydride (0.061 g, 1.53 mmol) and stirred at room temperature for 30 minutes. The solution is treated with methyl iodide (83 mL, 1.33 mmol) and warmed to room temperature over 4 hours. The reaction is quenched with ammonium chloride solution, diluted with ethyl acetate and separated. The organic layer is washed with brine (3x), dried (Na_2SO_4) and concentrated. The residue is purified by flash chromatography (5-10 % MeOH/CH₂Cl₂) to provide the title compound (0.31 g, 0.65 mmol). ¹H NMR (CD₃OD, 300 MHz) δ 8.55 (d, 1H), 7.99 (dd, 1H), 7.82 (m, 3H), 7.49 (dd, 1H), 7.43 (d, 1H), 6.55 (s, 1H), 4.75 (s, 2H), 3.96 (s, 2H), 3.52 (m, 4H), 3.86 (s, 3H), 3.49 (s, 3H). Ion Spray MS, $[M+H]^+$ =477.

The following compounds are prepared from starting materials obtained as described in Example 69 and the appropriate sulfonyl chlorides according to the method of Example 101.

Example	Name	m/z (M+H)
217	4-(3-Chlorobenzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one	460
218	4-(6-Chlorothieno[2,3-b]pyridine-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one.	462, 464 Cl pattern
219	4-(6-Bromobenzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one	505
220	2-[3-Oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazine-1-sulfonyl]-benzo[b]thiophene-6-carbonitrile	452
221	4-(5'-Chloro-[2,2']bithiophenyl-5-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one	493
222	4-[2-(4-Chlorophenyl)ethenesulfonyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one	431
223	{2-[4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazin-1-ylmethyl]pyrrolo[3,2-c]pyridin-1-yl} acetic acid	519, 521 Cl pattern

224	4-(5-Pyridin-4-ylthiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one	454
225	{2-[4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazin-1-ylmethyl]pyrrolo[3,2-c]pyridin-1-yl} acetic acid ethyl ester	547, 549 Cl pattern
226	4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-1-[1-(2-methoxyethyl)-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one	519, 520 Cl pattern
227	4-(6-Chlorothieno[3,2-b]pyridine-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one	462, 464 Cl pattern
228	{2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxopiperazin-1-ylmethyl]pyrrolo[2,3-c]pyridin-1-yl} acetic acid methyl ester	533, 535 Cl pattern
229	2-[3-Oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazine-1-sulfonyl]benzo[b]thiophene-5-carbonitrile	452
230	4-(5-Aminomethylbenzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one	456
231	2-{2-[4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-2-oxopiperazin-1-ylmethyl]pyrrolo[3,2-c]pyridin-1-yl}acetamide	518, 520 Cl pattern
232	4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-1-[1-(2-hydroxyethyl)-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one	505
233	4-(6-Chloro-1H-benzimidazole-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one	445, 447 Cl pattern
234	4-(1H-Benzimidazole-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one	411
235	4-(6-Aminomethyl-benzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one	456
236	1-(1H-Pyrrolo[3,2-c]pyridin-2-ylmethyl)-4-(thieno[2,3-b]pyridine-2-sulfonyl)piperazin-2-one	428
237	1-(1H-Pyrrolo[3,2-c]pyridin-2-ylmethyl)-4-(thieno[3,2-b]pyridine-2-sulfonyl)piperazin-2-one	428
238	4-[2-(5-Chloro-thiophen-2-yl)-ethanesulfonyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one	439, 441 Cl pattern
239	4-(2-Benzo[b]thiophen-2-yl-ethenesulfonyl)-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one	453
240	4-[2-(5-Chloro-4-methoxy-thiophen-2-yl)-ethenesulfonyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)piperazin-2-one	467, 469

241	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-furo[3,2-c]pyridin-2-ylmethyl-piperazin-2-one	462, 464
242	4-(6-Fluoro-benzo[b]thiophene-2-sulfonyl)-1-furo[3,2-c]pyridin-2-ylmethyl-piperazin-2-one	446
243	4-(6-Chlorobenzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[2,3-c]pyridin-2-ylmethyl)piperazin-2-one	460, 462 Cl pattern
244	4-(6-Chlorothieno[2,3-b]pyridine-2-sulfonyl)-1-(1H-pyrrolo[2,3-c]pyridin-2-ylmethyl)piperazin-2-one	462, 464 Cl pattern
245	{2-[4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-2-oxo-piperazin-1-ylmethyl]-pyrrolo[2,3-c]pyridin-1-yl}-acetic acid methyl ester	533, 535 Cl pattern
246	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-(1H-pyrrolo[3,2-b]pyridin-2-ylmethyl)-piperazin-2-one	461, 463 Cl pattern

EXAMPLE 247. 1-(4-Amino-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)piperazin-2-one.

A. (2-Chloro-pyridin-4-yl)-carbamic acid tert-butyl ester.

5 NaHMDS (61.7 mL, 1.0M solution in THF) is rapidly added to a solution of 2-chloro-pyridin-ylamine (4.0 g, 30.9 mmol) and BOC anhydride (6.74 g, 30.9 mmol) in THF (28 mL) at RT. The reaction mixture is cooled in an ice water bath (0°C) for 1h then stirred for 3 hr at RT. The gelatinous mixture is concentrated in vacuo and diluted with ethyl acetate and saturated NH₄Cl solution. The organic layer is washed with 0.1N HCl, saturated NaHCO₃ and brine. The 10 organic layer is then dried over MgSO₄, filtered and concentrated to dryness. The crude product is chromatographed eluting with 1% MeOH/CH₂Cl₂ to yield the title product (5.57 g, 24.4 mmol) as a yellow solid. ¹H NMR (CDCl₃, 300 MHz) δ 8.18 (d, 1H), 7.48 (d, 1H), 7.12 (dd, 1H), 1.60 (s, 9H). EI MS [M]⁺=228.

15 B. (2-Chloro-3-iodo-pyridin-4-yl)-carbamic acid tert-butyl ester.

tert-Butyllithium (36.3 mL, 1.7M in pentane) is added dropwise to a solution of (2-chloro-pyridin-4-yl)-carbamic acid tert-butyl ester (6.00 g, 26.2 mmol) in THF (46 mL) at -78 °C under Ar. The yellow/orange mixture is stirred for 2 h at -78°C then warmed to -40 °C for 1 h then cooled to -78°C before dropwise addition of I₂ (15.65 g, 61.7 mmol) in THF (49 mL). The reaction mixture is stirred for 1.5 h at -78°C then at -10°C for 30 minutes. The reaction is quenched with saturated NH₄Cl solution then diluted with CH₂Cl₂ and washed with saturated NH₄Cl, saturated sodium thiosulfate, water then brine. The organic layer is dried over MgSO₄, filtered and

concentrated to dryness. The crude product is chromatographed eluting with 1-2% MeOH/CH₂Cl₂ to yield the title product (7.96 g, 22.5 mmol) as a bright yellow solid. ¹H NMR (CDCl₃, 300 MHz) δ 8.14 (d, 1H), 8.02 (d, 1H), 7.32 (bs, 1H), 1.60 (s, 9H). EI MS [M]⁺=354, 356, Cl pattern.

5

C. 4-(4-Chloro-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-3-oxo-piperazine-1-carboxylic acid benzyl ester.

Trifluoroacetic acid (10 mL) is added to a solution of 2-(4-benzyloxycarbonyl-2-oxo-piperazin-1-ylmethyl)-4-chloro-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (5.66 g,

10 11.3 mmol, prepared in the same manner as described previously) in CH₂Cl₂ (10 mL). The solution is stirred overnight then diluted with CH₂Cl₂ and washed with saturated NaHCO₃ and brine. The organic layer is dried over MgSO₄, filtered and concentrated to dryness. The crude product is chromatographed eluting with 1-5% MeOH/CH₂Cl₂ to yield the title product (3.81 g, 9.56 mmol) as a foamy yellow solid.

15 ¹H NMR (CDCl₃, 300 MHz) δ 9.43 (bs, 1H), 8.08 (d, 1H), 7.38 (s, 5H), 7.18 (d, 1H), 6.51 (s, 1H), 5.15 (s, 2H), 4.58 (s, 2H), 4.20 (s, 2H), 3.71 (m, 2H), 3.50 (m, 2H). Ion spray [M+H]⁺= 399, 401, Cl pattern.

D. 4-(1-Benzenesulfonyl-4-chloro-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-3-oxo-piperazine-1-carboxylic acid benzyl ester.

Powdered NaOH (0.96 g, 23.9 mmol) followed by nBu₄NHSO₄ (0.32 g, 0.96 mmol) and benzene sulfonyl chloride (1.8 mL, 14.1 mmol) is added to a solution of 4-(4-chloro-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-3-oxo-piperazine-1-carboxylic acid benzyl ester (3.81 g, 9.56 mmol) in CH₂Cl₂ (32 mL) at RT. The resulting slurry is stirred for 3.5 h then diluted with CH₂Cl₂, 25 and washed with saturated NaHCO₃ and brine. The organic layer is dried over MgSO₄, filtered and concentrated to dryness. The crude product is chromatographed eluting with 1-5% MeOH/CH₂Cl₂ to yield the title product (5.06 g, 9.38 mmol). ¹H NMR (CDCl₃, 300 MHz) δ 8.23 (d, 1H), 7.97 (d, 1H), 7.84 (d, 2H), 7.61 (d, 1H), 7.51 (m, 2H), 7.38 (s, 5H), 6.50 (s, 1H), 5.18 (s, 2H), 5.03 (s, 2H), 4.29 (s, 2H), 4.29 (s, 2H), 3.80 (m, 2H), 3.51 (m, 2H). Ion spray [M+H]⁺= 539, 30 541, Cl pattern.

E. 1-(1-Benzenesulfonyl-4-chloro-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.

TMSI (2.7 mL, 19.0 mmol) is added to a solution of 4-(1-benzenesulfonyl-4-chloro-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-3-oxo-piperazine-1-carboxylic acid benzyl ester (5.06 g, 9.38 mmol) in CH₃CN (134 mL) at 0°C. The reaction mixture is warmed to RT and stirred for 5

hours. The reaction mixture is concentrated to dryness and the red residue is diluted with MeOH and concentrated to dryness (this is repeated twice). The mixture is diluted with CH₂Cl₂ and washed with saturated NaHCO₃ and brine. The organic layer is dried over MgSO₄, filtered and concentrated to dryness. The crude product is chromatographed eluting with 1-5% MeOH/CH₂Cl₂ to yield the title product (0.70 g, 1.74 mmol) and unreacted starting material (3.58 g, 6.64 mmol). ¹H NMR (CDCl₃, 300 MHz) δ 8.20 (d, 1H), 7.93 (d, 1H), 7.85 (d, 2H), 7.60 (d, 1H), 7.51 (m, 2H), 6.50 (s, 1H), 5.01 (s, 2H), 3.45 (m, 2H), 3.18 (m, 2H). Ion spray [M+H]⁺= 405, 407, Cl pattern.

10 **F. 1-(4-Amino-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-4-(6-chlorobenzo[b]thiophene-2-sulfonyl)piperazin-2-one.**

Anhydrous ammonium acetate (0.56 g, 7.2 mmol), phenol (0.45 g, 4.8 mmol) and 1-(1-benzenesulfonyl-4-chloro-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one (0.31 g, 0.48 mmol, prepared as described previously) are heated to 100°C for 3.5 days. The mixture is cooled to RT then the crude product is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 100% CH₃CN then the appropriate product fractions are lyophilized to provide the title compound (1.29 g, 2.2 mmol) as a white solid (22.4 mg, 0.038 mmol). ¹H NMR (DMSO-d₆, 300 MHz) δ 12.40 (bs, 1H), 12.00 (bs, 1H), 8.31 (d, 1H), 8.20 (s, 1H), 8.06 (d, 1H), 8.02 (bs, 2H), 7.57 (dd, 1H), 7.48 (m, 1H), 6.89 (d, 1H), 6.81 (s, 1H), 4.60 (s, 2H), 3.81 (s, 2H), 3.40 (m, 4H). LR-FAB MS, [M+H]⁺=476, 478.

EXAMPLE 248. 4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-5-(±)-hydroxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.

25 **A. 2-[4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-2-(±)-hydroxymethyl-6-oxo-piperazin-1-ylmethyl]-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester.**

Sodium borohydride (0.005 g, 0.13 mmol) is added to a solution of 2-[4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-2-(±)-methoxycarbonyl-6-oxo-piperazin-1-ylmethyl]-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (0.04 g, 0.07 mmol), (prepared from 2-(2-(±)-methoxycarbonyl-6-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester, EXAMPLE 71, and 2-(5-chloro-thiophen-2-yl)-ethenesulfonyl chloride, EXAMPLE 3, using the procedure described in EXAMPLE 214, Part A) in MeOH (3 mL) at RT. The reaction mixture is stirred for 6 h then quenched with water and concentrated in vacuo. The crude product (0.04 g) is taken onto the next step without further purification.

B. 4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-5-(\pm)-hydroxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.

Trifluoroacetic acid (1.8 mL) is added to a solution of 2-[4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-2-(\pm)-hydroxymethyl-6-oxo-piperazin-1-ylmethyl]-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (0.04 g) in CH_2Cl_2 (4.2 mL) at RT. The reaction mixture is stirred for 4 h then concentrated in vacuo. The title compound is purified by RP-HPLC eluting in a gradient of 10% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (0.1% TFA) to 100% CH_3CN and lyophilizing the appropriate product fractions. ^1H NMR (DMSO- d_6 , 300 MHz) δ 9.10 (s, 1H), 8.46 (d, 1H), 7.82 (d, 1H), 7.50 (d, 1H) 7.43 (d, 1H), 7.14 (d, 1H), 7.01 (d, 1H), 6.94 (s, 1H), 5.12 (bs, 1H), 4.80 (AB, 2H), 3.98 (d, 2H), 3.90 (m, 1H), 3.40-3.50 (m, 4H). APCI MS, $[\text{M}+\text{H}]^+=467, 469$.

The following compounds are prepared from starting materials obtained using the methods of Examples 69, 70 and 71 and the appropriate sulfonyl chlorides according to the method of Example 101.

Example	Name	m/z
249	1-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-5-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-(\pm)-carboxylic acid methyl ester	519, 521 Cl pattern
250	1-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-5-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-(\pm)-carboxylic acid methyl ester	495, 497 Cl pattern
251	1-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-5-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-(\pm)-carboxylic acid	505, 507 Cl pattern
252	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-5-(\pm)-hydroxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	491, 493 Cl pattern

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The following enantiomerically pure compounds are obtained by chiral resolution on a CHIRACEL OD prep column.

Example	Name	%ee	m/z
253	1-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-5-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-($-$)-carboxylic acid methyl ester	99% (-)	495, 497 Cl pattern

254	1-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-5-oxo-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-(+)-carboxylic acid methyl ester	95% (+)	495, 497 Cl pattern
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EXAMPLE 255. 4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-(R)-hydroxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.

A. 6-(R)-(tert-Butyl-dimethyl-silanyloxymethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.

5 Trifluoroacetic acid (0.25 mL) is added to a solution of 2-(R)-(tert-butyl-dimethyl-silanyloxymethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-6-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (0.025 g, 0.037 mmol) in CH_2Cl_2 (0.5 mL) at room temperature. The reaction mixture is stirred for 2 h then concentrated to dryness. The 10 residue is diluted with CH_2Cl_2 and washed with saturated NaHCO_3 and brine. The organic layer is dried over MgSO_4 , filtered and concentrated in vacuo. The crude product (0.019 g, 0.033 mmol) is used in the subsequent step without further purification.

15 B. 4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-(R)-hydroxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.

Glacial acetic acid (3 mL, 0.046 mmol) and tetrabutylammonium fluoride (92 mL, 0.092 mmol) is added to a solution of 6-(R)-(tert-butyl-dimethyl-silanyloxymethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one (0.019 g, 0.033 mmol) in THF (0.5 mL). The resulting solution is stirred for 4 h then concentrated in 20 vacuo. The crude product is purified by RP-HPLC eluting in a gradient of 10% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (0.1% TFA) to 100% CH_3CN and the appropriate product fractions are lyophilized to provide the title compound (0.009 g, 0.016 mmol) as a white solid. ^1H NMR (DMSO-d_6 , 300 MHz) δ 14.50 (bs, 1H), 12.60 (bs, 1H), 9.18 (s, 1H), 8.38 (d, 1H), 7.89 (d, 1H), 7.61 (d, 1H), 7.50 (d, 1H), 7.21 (d, 1H), 7.08 (d, 1H), 6.90 (s, 1H), 5.03 (s, 2H), 4.63 (d, 2H), 3.70-3.90 (AB, 2H), 3.75 (m, 1H), 25 3.21 (m, 2H). Ion spray MS, $[\text{M}+\text{H}]^+=467, 469$, Cl pattern.

The following compounds are prepared from starting materials obtained as described in Examples 69, 70 and 71 and the appropriate sulfonyl chloride according to the method of Example 101.

Example	Name	m/z
256	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-(R)-hydroxymethyl-1-(1H-	491, 493

	pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	
257	4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-(±)-carboxylic acid methyl ester	495, 497 Cl pattern
258	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-(±)-carboxylic acid methyl ester	519, 521 Cl pattern
259	4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-(±)-carboxylic acid	481, 483 Cl pattern
260	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-(±)-carboxylic acid	505, 507 Cl pattern
261	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-(±)-hydroxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	491, 493 Cl pattern
262	4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-6-(±)-hydroxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	467, 469 Cl pattern
263	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazine-2-(±)-carboxylic acid amide	504, 506 Cl pattern
264	4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	481, 483
265	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	505, 507
266	4-(5'-Chloro-[2,2']bithiophenyl-5-sulfonyl)-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	537, 539
267	4-[2-(4-Chloro-phenyl)-ethenesulfonyl]-3-(S)-methoxymethyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	475, 477

EXAMPLE 268. 1-(4-Aminoquinazolin-7-ylmethyl)-4-(6-chlorobenzo[b]thiophene-2-ylmethyl)piperazin-2-one.

To a solution of 1-(4-aminoquinazoline-7-ylmethyl)piperazine-2-one bishydrochloride (1.84 g, 5.73 mmol), EXAMPLE 72, in DMF (20 mL) is added 2-bromomethyl-6-chlorobenzo[b]thiophene, EXAMPLE 5, (1.5 g, 5.73 mmol) and K_2CO_3 (4.0 g, 28.7 mmol). The

solution is stirred for 16 hours. After this time, the solution is diluted with water. The solution is acidified with trifluoroacetic acid. The product is purified by RP-HPLC eluting in a gradient of 10% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (0.1% TFA) to 50% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (0.1% TFA). The appropriate collected fractions are lyophilized to afford the title compound as a white solid. ^1H NMR (d^6 -DMSO, 300MHz) δ 9.78 (bs, 3H), 8.82 (s, 1H), 8.34 (d, 1H), 8.07 (s, 1H), 7.81 (d, 1H), 7.63 (d, 1H), 7.51 (s, 1H), 7.32 (m, 2H), 4.71 (s, 2H), 3.95 (s, 2H), 3.28 (m, 4H), 2.80 (m, 2H).

EXAMPLE 269. 1-(4-Aminoquinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazol-2-ylmethyl)piperazin-2-one.

A mixture of 1-(4-aminoquinazolin-7-ylmethyl)piperazin-2-one (50 mg, 0.15 mmol), EXAMPLE 72, 6-chloro-2-chloromethylbenzimidazole (30.5 mg, 0.15 mmol) and potassium carbonate (83 mg, 0.6 mmol) in 2 mL of DMF is stirred at ambient temperature overnight. The mixture is purified on reverse phase HPLC ($\text{CH}_3\text{CN}/\text{H}_2\text{O}/\text{TFA}$) to give the trifluoroacetic acid salt of 1-(4-aminoquinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazol-2-ylmethyl)piperazin-2-one (25 mg) as a solid. ^1H NMR (CD_3OD , 300 MHz) δ 8.69 (s, 1H), 8.33 (d, 1H), 7.79 (s, 1H), 7.75-7.69 (m, 3H), 7.57-7.54 (m, 1H), 4.86 (s, 2H), 4.22 (s, 2H), 3.31 (m, 4H), 2.99 (m, 2H). MS m/z 422 (M+H).

EXAMPLE 270. 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzothioazol-2-ylmethyl)-piperazin-2-one.

To a solution of 1-(4-amino-quinazolin-7-ylmethyl)-piperazin-2-one (76 mg, 0.23 mmol), EXAMPLE 72, in 2 mL of DMF is added potassium carbonate (127 mg, 0.92 mmol) followed by 6-chloro-2-chloromethyl-benzothiazole (prepared according to the procedure of B.L.Mylari, Synthesis Comm. 1989, 16, 2921) (50 mg, 0.23 mmol). The resulting mixture is stirred overnight at room temperature. The undissolved potassium carbonate is removed by filtration and the mother liquor is purified by reverse phase HPLC (10-100% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$). The desired product is obtained as a white solid with a melting point of 123-126°C. $\text{C}_{21}\text{H}_{19}\text{ClN}_6\text{OS}$ MS m/z: 439, 441. Anal. calcd. for $\text{C}_{21}\text{H}_{19}\text{ClN}_6\text{OS} \cdot 2\text{C}_2\text{HF}_3\text{O}_2$: C, 45.02; H, 3.17 N, 12.60. Found C, 44.15; H, 3.19; N, 11.79.

EXAMPLE 271. 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzooxazol-2-ylmethyl)-piperazin-2-one.

The desired product (10.0 mg, 7 %) is isolated as a white solid. $\text{C}_{21}\text{H}_{19}\text{ClN}_6\text{O}_2$ MS m/z: 423, 425.

EXAMPLE 272. 1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-benzothioazol-2-ylmethyl)-piperazin-2-one.

The desired product (19.0 mg, 22%) is obtained as a white solid. $C_{21}H_{19}ClN_6OS$ MS m/z: 438,440. Anal. cald. for $C_{21}H_{19}ClN_6OS \cdot 2C_2HF_3O_2$: C, 45.02; H, 3.17 N, 12.60. Found C, 43.35; H, 3.26; N, 12.65.

EXAMPLE 273. 3-[4-(4-Aminoquinazoline-7-ylmethyl)-3-oxopiperazin-1-ylmethyl]-7-chloro-1H-quinolin-2-one.

The title compound is prepared as described in EXAMPLE 268, substituting 3-bromomethyl-7-chloro-1H-quinoline-2-one, EXAMPLE 8, for 2-bromomethyl-6-chlorobenzo[b]thiophene. The product is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 50% CH_3CN/H_2O (0.1% TFA). The appropriate collected fractions are lyophilized to afford the title compound as a white solid.

1H NMR (d_6 -DMSO, 300MHz) δ 12.18 (bs, 1H), 9.75 (m, 1H), 8.86 (s, 1H), 8.40 (m, 1H), 8.11 (d, 1H), 8.10 (s, 1H), 7.78 (m, 1H), 7.69 (m, 2H), 7.37 (m, 1H), 4.80 (s, 2H), 4.10 (m, 2H), 3.47 (m, 4H), 3.30 (m, 2H). MS (ion spray) m/z 449, (M+H).

EXAMPLE 274. 1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-chloro-1H-indol-6-ylmethyl)-piperazin-2-one.

A. 1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-chloro-1-(toluene-4-sulfonyl)-1H-indol-6-ylmethyl)-piperazin-2-one.

The title compound is prepared as described in EXAMPLE 268 using 6-bromomethyl-3-chloro-1-(toluene-4-sulfonyl)-1H-indole, EXAMPLE 16, in place of 2-bromomethyl-6-chlorobenzo[b]thiophene. The crude material is purified by RP-HPLC eluting in a gradient of 10% CH_3CN/H_2O (0.1% TFA) to 80% CH_3CN/H_2O (0.1% TFA) and the appropriate product fractions are combined and lyophilized to give a white solid. 1H NMR (DMSO- d_6 , 300 MHz) δ 9.75 (bs, 2H), 8.82 (s, 1H), 8.40 (d, 1H), 7.64 (m, 2H), 7.60 (m, 2H), 7.40 (d, 1H), 7.23 (m, 1H), 7.19 (m, 2H), 6.99 (d, 2H), 5.09 (s, 2H), 4.78 (s, 2H), 4.10 (m, 2H), 3.40 (m, 4H), 2.49 (s, 3H).

B. 1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-chloro-1H-indol-6-ylmethyl)-piperazin-2-one.

To a solution of 1-(4-amino-quinazolin-7-ylmethyl)-4-(3-chloro-1-(toluene-4-sulfonyl)-1H-indol-6-ylmethyl)-piperazin-2-one ditrifluoroacetate (31 mg, 0.04 mmol) in 2 mL of MeOH is added 0.3 mL of 1N NaOH solution. The solution is heated at 100°C for 3 hours. After this time, the solution is diluted with water/acetonitrile and neutralized with trifluoroacetic acid. The

crude material is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are combined and lyophilized to give the title compound (21 mg, 0.03 mmol) as a white solid. ¹H NMR (DMSO-d₆, 300 MHz) δ 9.71 (bs, 2H), 8.81 (s, 1H), 8.40 (d, 1H), 7.63 (m, 3H), 7.53 (d, 1H), 7.50 (s, 1H), 5.20 (d, 1H), 4.78 (s, 2H), 4.30-3.10 (m, 8H). ESI MS, [M+H]⁺=421, 423 (Cl pattern).

EXAMPLE 275. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-(E)-allyl]-piperazin-2-one.

To a solution of 1-(4-amino-quinazolin-7-ylmethyl)-piperazin-2-one bishydrochloride (100 mg, 0.31 mmol), EXAMPLE 72, in 3 mL of DMF is added 2-(3-bromo-(E)-propenyl)-5-chloro-thiophene (73 mg, 0.31 mmol), prepared as described in EXAMPLE 17., and K₂CO₃ (0.21 g, 1.54 mmol). The solution is stirred at room temperature for 16 hours. After this time, the solution is diluted with water/acetonitrile and neutralized with trifluoroacetic acid. The crude material is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are combined and lyophilized to give the title compound (80 mg, 0.12 mmol) as a white solid. ¹H NMR (DMSO-d₆, 300 MHz) δ 9.76 (bs, 2H), 8.81 (s, 1H), 8.40 (d, 1H), 7.70 (s, 1H), 7.62 (dd, 1H), 7.10 (m, 2H), 6.90 (d, 1H), 6.05 (dt, 1H), 4.80 (s, 2H), 3.77 (m, 4H), 3.50 (m, 2H), 3.37 (m, 2H). ESI MS, [M+H]⁺=414,416 (Cl pattern). Anal. (C₂₀H₂₀CIN₅OS·2.0TFA·1.1H₂O) C, H, N.

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EXAMPLE 276. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-but-2-(E)-enyl]-piperazin-2-one ditrifluoroacetate.

¹H NMR (DMSO-d₆, 300 MHz) δ 9.70 (bs, 2H), 8.82 (s, 1H), 8.40 (d, 1H), 7.68 (s, 1H), 7.61 (d, 1H), 7.10 (m, 2H), 5.88 (t, 1H), 4.79 (s, 2H), 3.75 (m, 4H), 3.49 (m, 2H), 3.29 (m, 2H), 25 2.09 (s, 3H). EI MS, [M+H]⁺=427, 429 (Cl pattern).

EXAMPLE 277. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-2-methyl-(E)-allyl]-piperazin-2-one ditrifluoroacetate.

¹H NMR (DMSO-d₆, 300 MHz) δ 9.80 (bs, 2H), 8.85 (s, 1H), 8.41 (d, 1H), 7.70 (s, 1H), 30 7.68 (d, 1H), 7.06 (d, 1H), 7.05 (d, 1H), 6.70 (bs, 1H), 4.80 (s, 2H), 4.30 (bs, 2H), 3.45 (m, 4H), 3.10 (m, 2H), 1.99 (s, 3H). ESI MS, [M+H]⁺=428, 430 (Cl pattern).

EXAMPLE 278. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-furan-2-yl)-(E)-allyl]-piperazin-2-one.

To a solution of 1-(4-amino-quinazolin-7-ylmethyl)-piperazin-2-one (50 mg, 0.20 mmol), EXAMPLE 72, in 3 mL of acetonitrile is added 3-(4-bromo-furan-2-yl)-(E)-propenal (43 mg, 0.22 mmol), prepared as described in EXAMPLE 18, 2 drops of HOAc and sodium triacetoxyborohydride (62 mg, 0.29 mmol). The solution is stirred at room temperature for 16 hours. After this time, the solution is diluted with water/acetonitrile. The crude material is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 80% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are combined and lyophilized to give the title compound (48 mg, 0.07 mmol) as a white solid. ¹H NMR (DMSO-d₆, 300 MHz) δ 9.75 (bs, 2H), 8.85 (s, 1H), 8.60 (d, 1H), 7.95 (s, 1H), 7.69 (s, 1H), 7.62 (d, 1H), 6.80 (s, 1H), 6.65 (d, 1H), 6.19 (dt, 1H), 4.80 (s, 2H), 3.70 (m, 4H), 3.50 (m, 2H), 3.28 (m, 2H). ESI MS, [M+H]⁺=441,443 (Br pattern).

EXAMPLE 279. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(6-methoxy-pyridin-3-yl)-(E)-allyl]-piperazin-2-one.

Nitrogen (g) is bubbled through a solution of 1-(4-amino-quinazolin-7-ylmethyl)-piperazin-2-one (100 mg, 0.39 mmol), EXAMPLE 72, in 2 mL of CH₃CN. After 5 min, acetic acid 3-(6-methoxy-pyridin-3-yl)-(E)-allyl ester (75 mg, 0.36 mmol, prepared as described in EXAMPLE 19 in 2 mL of CH₃CN, palladium(II) acetate (catalytic amount), triphenylphosphine (catalytic amount), 2 mL of H₂O and 0.5 mL of triethylamine are added to the solution. The mixture is heated at 80°C for 1 hours. At this time, the mixture is cooled, filtered and concentrated in vacuo. The crude material is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are combined and lyophilized to give the title compound (44 mg, 0.07 mmol) as a white solid. ¹H NMR (DMSO-d₆, 300 MHz) δ 9.86 (s, 1H), 9.79 (s, 1H), 8.83 (s, 1H), 8.40 (d, 1H), 8.25 (s, 1H), 7.95 (d, 1H), 7.75 (s, 1H), 7.63 (d, 1H), 6.86 (d, 1H), 6.82 (d, 1H), 6.32 (dt, 1H), 4.78 (s, 2H), 3.98 (s, 2H), 3.93 (m, 2H), 3.85 (s, 3H), 3.53 (m, 4H). ESI MS, [M+H]⁺=405.

EXAMPLE 280. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-(E)-allyl]-4-oxy-piperazin-2-one.

To a solution of 1-(4-amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-(E)-allyl]-piperazin-2-one ditrifluoroacetate (0.60 g, 0.94 mmol), prepared as described in EXAMPLE 275, in 25 mL of CH₂Cl₂ is added m-chloroperoxybenzoic acid (0.30 g, 0.96 mmol, 55% pure grade). The mixture is stirred at room temperature for 3 h and then concentrated in vacuo. The crude material is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are

combined and lyophilized to give the title compound (0.5 mg, 0.76 mmol) as a white solid. ¹H NMR (DMSO-d₆, 300 MHz) δ 9.68 (bs, 2H), 8.79 (s, 1H), 8.39 (d, 1H), 7.68 (s, 1H), 7.60 (d, 1H), 7.17 (d, 1H), 7.12 (d, 1H), 7.06 (d, 1H), 6.17 (dt, 1H), 4.84 (s, 2H), 4.53 (m, 2H), 4.50 (AB, 2H), 4.04 (m, 2H), 3.78 (m, 1H), 3.60 (m, 1H). ESI MS, [M+H]⁺=430,432 (Cl pattern).

5 Anal. (C₂₀H₂₀CIN₅O₂S·2.0TFA·1.4H₂O) C, H, N.

EXAMPLE 281. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-prop-2-ynyl]-piperazin-2-one.

The title compound is prepared as described in EXAMPLE 275 using 2-(3-bromo-prop-1-ynyl)-5-chloro-thiophene (prepared as described in EXAMPLE 20) in place of 2-(3-bromo-(E)-propenyl)-5-chloro-thiophene. The crude material is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 70% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are combined and lyophilized to give the title compound as a white solid. ¹H NMR (DMSO-d₆, 300 MHz) δ 9.77 (bs, 2H), 8.83 (s, 1H), 8.38 (d, 1H), 7.63 (d, 1H), 7.58 (s, 1H), 7.25 (d, 1H), 7.13 (d, 1H), 4.74 (s, 2H), 3.74 (s, 2H), 3.32 (m, 4H), 2.85 (m, 2H). ESI MS, [M+H]⁺=412, 414 (Cl pattern).

EXAMPLE 282. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-propyl]-piperazin-2-one

The title compound is prepared as described in EXAMPLE 278 using 3-(5-chloro-thiophen-2-yl)-propionaldehyde (EXAMPLE 28, Part A) in place of 3-(4-bromo-furan-2-yl)-(E)-propenal. The crude material is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are combined and lyophilized to give the title compound as a white solid. ¹H NMR (DMSO-d₆, 300 MHz) δ 9.77 (bs, 2H), 8.81 (s, 1H), 8.39 (d, 1H), 7.71 (s, 1H), 7.60 (d, 1H), 6.95 (d, 1H), 6.77 (d, 1H), 4.78 (s, 2H), 3.88 (m, 2H), 3.50 (m, 2H), 3.42 (m, 2H), 3.05 (m, 2H), 2.80 (t, 2H), 1.96 (m, 2H). ESI MS, [M+H]⁺=416,418 (Cl pattern).

EXAMPLE 283. 1-(4-Amino-quinazolin-7-ylmethyl)-4-prop-2-ynyl-piperazin-2-one:

30 A. 1-(4-Amino-quinazolin-7-ylmethyl)-4-prop-2-ynyl-piperazin-2-one.

Propargyl bromide (0.29 g, 1.95 mmol) is added to a solution containing 1-(4-amino-quinazolin-7-ylmethyl)-piperazin-2-one (0.5 g, 1.95 mmol), EXAMPLE 72, and K₂CO₃ (0.40 g, 2.93 mmol) in DMSO (10 mL) at ambient temperature. After 15 min, the reaction mixture is partitioned between aqueous NaHCO₃ (100 mL) and CH₂Cl₂ (100 mL) and the layers are separated. The aqueous phase is subsequently saturated with NaCl and extracted three times

with CHCl_3 (50 mL). The combined organic phase is washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated. The residue is purified by flash silica gel chromatography (CH_2Cl_2 to 10% $\text{MeOH}/\text{CH}_2\text{Cl}_2$) to provide 390 mg (68%) of the title compound as a white solid.
5 ^1H NMR (300 MHz, CDCl_3) δ 2.68 (m, 1H), 3.13-3.37 (m, 6H), 4.07 (app q, J = 5.2 Hz, 1H), 4.63 (s, 2H), 7.28 (dd, J = 8.4, 1.4 Hz, 1H), 7.42 (s, 1H), 7.72 (br s, 2H), 8.14 (d, J = 8.4 Hz, 1H), 8.34 (s, 1H) ppm; MS (ISP loop): m/z 296 (M+H).

EXAMPLE 284. 1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-biphenyl-2-yl-prop-2-ynyl)-piperazin-2-one.

10 A solution containing 1-(4-amino-quinazolin-7-ylmethyl)-4-prop-2-ynyl-piperazin-2-one (50 mg, 0.17 mmol), EXAMPLE 283, 2-bromobiphenyl (44 mg, 0.19 mmol), Et_3N (69 mg, 0.68 mmol), $(\text{Ph}_3\text{P})_4\text{PdCl}_2$ (6 mg, 0.008 mmol), and CuI (1 mg, 0.005 mmol) in anhydrous DMF (2 mL) is warmed at 80°C for 1 hours. The reaction mixture is cooled to 50 °C and the solvent is removed over 16 h under a stream of nitrogen. The crude residue is purified by flash silica gel chromatography (CH_2Cl_2 to 10% $\text{MeOH}/\text{CH}_2\text{Cl}_2$) to afford a colorless gum which is triturated with ethyl alcohol to provide 4 mg (5%) of the title compound as a white solid. ^1H NMR (300 MHz, $d_6\text{-DMSO}$) δ 3.03 (s, 2H), 3.14 (m, 2H), 3.31 (m, 2H), 3.50 (s, 2H), 7.21-7.55 (m, 11H), 7.76 (br s, 2H), 8.18 (d, J = 8.6 Hz, 1H), 8.36 (s, 1H) ppm; MS (ion spray): m/z 448 (M+H).

20 EXAMPLE 285. 1-(4-Amino-quinazolin-7-ylmethyl)-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.

A. (3-{3-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-prop-1-ynyl}-pyridin-4-yl)-carbamic acid tert-butyl ester.

25 A solution containing 1-(4-amino-quinazolin-7-ylmethyl)-4-prop-2-ynyl-piperazin-2-one (100 mg, 0.34 mmol), EXAMPLE 283, (3-iodo-pyridin-4-yl)-carbamic acid tert-butyl ester, EXAMPLE 69, Part B, (108 mg, 0.34 mmol), Et_3N (140 mg, 1.36 mmol), $(\text{Ph}_3\text{P})_4\text{PdCl}_2$ (12 mg, 0.017 mmol), and CuI (2 mg, 0.01 mmol) in anhydrous DMF (5 mL) is stirred at ambient temperature. After 5 h, the reaction mixture is diluted with EtOAc (50 mL) and water (50 mL) and the layers are separated. The aqueous layer is extracted twice with EtOAc (25 mL) and the combined organic phase is washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated. The crude residue is purified by flash silica gel chromatography (CH_2Cl_2 to 10% $\text{MeOH}/\text{CH}_2\text{Cl}_2$) to provide 59 mg (36%) of the title compound as a colorless oil. ^1H NMR (300 MHz, CDCl_3) δ 1.49 (s, 9H), 2.84 (m, 2H), 3.35 (m, 2H), 3.44 (s, 2H), 3.71 (s, 2H), 4.75 (s, 2H), 6.19 (br s, 2H), 7.24 (d, J = 5.5 Hz, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.66 (s, 1H), 7.79 (d, J = 8.4

Hz, 1H), 8.05 (d, J = 5.5 Hz, 1H), 8.37 (s, 1H), 8.49 (s, 1H), 8.58 (s, 1H) ppm; MS (ISP loop): m/z 488 (M+H).

B. 2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester.

5 1,8-Diazabicyclo[5.4.0]undec-7-ene (37 mg, 0.24 mmol) is added to a suspension containing (3-[3-[4-(4-amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-prop-1-ynyl]-pyridin-4-yl)-carbamic acid tert-butyl ester (59 mg, 0.12 mmol) in anhydrous CH_3CN (5 mL) and the mixture is warmed to 50 °C. Dimethylformamide (1 mL) is added to solubilize and the 10 homogeneous solution is maintained for 5 h at 50°C. The reaction mixture is diluted with EtOAc (50 mL) and water (50 mL) and the layers are separated. The aqueous layer is extracted twice with EtOAc (25 mL) and the combined organic phase is washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated to provide 50 mg of the product as a crude solid which is used directly without further purification. ^1H NMR (300 MHz, CDCl_3) δ 1.64 (s, 9H), 15 2.78 (m, 2H), 3.30 (m, 2H), 3.37 (s, 2H), 3.95 (s, 2H), 4.74 (s, 2H), 6.24 (br s, 2H), 6.63 (s, 1H), 7.40 (dd, J = 8.5, 1.6 Hz, 1H), 7.64 (s, 1H), 7.81 (d, J = 5.8 Hz, 1H), 7.83 (d, J = 8.5 Hz, 1H), 7.99 (s, 1H), 8.39 (d, J = 5.8 Hz, 1H), 8.58 (s, 1H), 8.77 (s, 1H) ppm.

C. 1-(4-Amino-quinazolin-7-ylmethyl)-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.

20 To a solution containing 2-[4-(4-amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (50 mg, 0.12 mmol) in CH_2Cl_2 (5 mL) is added TFA (1 mL) at ambient temperature. After 16 h, the reaction mixture is concentrated to dryness, diluted with water and purified by reverse-phase HPLC [Buffer A: water w/ 0.1% TFA; Buffer B: CH_3CN w/ 0.1% TFA; Gradient: 0% B to 45% B over 30 min] to 25 provide 34 mg (73%, two steps) of the title compound as a white, lyophilized solid. ^1H NMR (300 MHz, CDCl_3) δ 2.77 (s, 3H), 3.23 (s, 2H), 3.31 (m, 2H), 3.89 (s, 2H), 4.00 (br s, 3H), 4.71 (s, 2H), 6.94 (s, 1H), 7.60 (m, 2H), 7.84 (d, J = 6.5 Hz, 1H), 8.36 (m, 2H), 8.81 (s, 1H), 9.18 (s, 1H), 9.73 (br s, 2H), 12.87 (s, 1H) ppm; MS (ion spray): m/z 388 (M+H).

30 The following compounds are prepared from the compound of Example 72 using the procedures described above.

Example	Name	m/z (M+H)
286	1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yloxy)-ethyl]-piperazin-2-one	418, 420 Cl pattern
287	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1-methyl-1H-indol-2-	435, 437

	ylmethyl)-piperazin-2-one	Cl pattern
288	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-allyl]-piperazin-2-one	414, 416 Cl pattern
289	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(6-chloro-benzo[b]thiophen-2-yl)-allyl]-piperazin-2-one	464, 466 Cl pattern
290	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-4-methyl-thiophen-2-yl)-allyl]-piperazin-2-one	428, 430 Cl pattern
291	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-benzofuran-2-ylmethyl)-piperazin-2-one	422, 424 Cl pattern
292	1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-chloro-1H-indol-5-ylmethyl)-piperazin-2-one	421, 423 Cl pattern
293	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-piperazin-2-one	421, 423 Cl pattern
294	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5,7-dichloro-1H-indol-2-ylmethyl)-piperazin-2-one	455, 457 Cl pattern
295	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-indol-2-ylmethyl)-piperazin-2-one	421, 423 Cl pattern
296	1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-p-tolyl-prop-2-ynyl)-piperazin-2-one	386
297	1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-m-tolyl-prop-2-ynyl)-piperazin-2-one	386
298	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-phenyl)-prop-2-ynyl]-piperazin-2-one	406, 408 Cl pattern
299	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-chloro-phenyl)-prop-2-ynyl]-piperazin-2-one	406, 408 Cl pattern
300	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(2-chloro-phenyl)-prop-2-ynyl]-piperazin-2-one	406
301	1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-biphenyl-4-yl-prop-2-ynyl)-piperazin-2-one	448
302	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4,5-dibromo-thiophen-2-yl)-allyl]-piperazin-2-one	536, 538, 540 Br ₂ pattern
303	1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-biphenyl-3-yl-prop-2-ynyl)-piperazin-2-one	448

304	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(2,5-dichloro-thiophen-3-yl)-prop-2-ynyl]-piperazin-2-one	446, 448 Cl pattern
305	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-chloro-phenyl)-propyl]-piperazin-2-one	410, 412 Cl pattern
306	1,4-Bis-(4-amino-quinazolin-7-ylmethyl)-piperazin-2-one	415
307	1-(4-Amino-quinazolin-7-ylmethyl)-4-(1H-pyrrolo[2,3-c]pyridin-2-ylmethyl)-piperazin-2-one	388
308	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-nitro-thiophen-2-yl)-allyl]-piperazin-2-one	425
309	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(6-chloro-pyridin-3-yl)-allyl]-piperazin-2-one	409, 411 Cl pattern
310	1-(4-Amino-quinazolin-7-ylmethyl)-4-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one	388
311	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-3-yl)-allyl]-piperazin-2-one	414, 416 Cl pattern
312	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-bromo-furan-2-yl)-allyl]-piperazin-2-one	442, 444 Br pattern
313	1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(5-methyl-thiophen-2-yl)-penta-2,4-dienyl]-piperazin-2-one	420
314	1-(4-Amino-quinazolin-7-ylmethyl)-4-(2-chloro-benzo[b]thiophen-5-ylmethyl)-piperazin-2-one	438, 440 Cl pattern
315	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-methyl-thiophen-2-yl)-allyl]-piperazin-2-one	394
316	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-methoxy-thiophen-2-yl)-allyl]-piperazin-2-one	410
317	4-(1-Amino-7-chloro-isoquinolin-3-ylmethyl)-1-(4-amino-quinazolin-7-ylmethyl)-piperazin-2-one	448, 450 Cl pattern
318	2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-N-(5-chloro-thiophen-2-yl)-acetamide	431
319	1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-piperazin-2-one	433, 435 Cl pattern
320	1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(3-chloro-phenyl)-2-(S)-hydroxy-ethyl]-piperazin-2-one	412, 414 Cl pattern
321	1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(3-chloro-phenylsulfanyl)-	428, 430

	ethyl]-piperazin-2-one	Cl pattern
322	1-(4-Amino-quinazolin-7-ylmethyl)-4-(2-methylene-1,1-dioxo-2,3-dihydro-1H-1I 6-bénzo[b]thiophen-3-yl)-piperazin-2-one	470
323	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-nitro-phenyl)-allyl]-piperazin-2-one	419
324	1-(4-Amino-quinazolin-7-ylmethyl)-4-(2-chloro-benzo[b]thiophen-6-ylmethyl)-piperazin-2-one	438, 440 Cl pattern
325	2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-N-(4-chloro-phenyl)-acetamide	425, 427 Cl pattern
326	1-(4-Amino-quinazolin-7-ylmethyl)-4-[1-(4-chloro-phenyl)-pyrrolidin-3-yl]-piperazin-2-one	437, 439 Cl pattern
327	1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethyl]-piperazin-2-one	402, 404 Cl pattern
328	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-phenyl)-propyl]-piperazin-2-one	410, 412 Cl pattern
329	2-[4-(4-Aminoquinazoline-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-3-(4-chlorophenyl)-acrylic acid	452, 454 Cl pattern
330	1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-1-hydroxy-isoquinolin-3-ylmethyl)-piperazin-2-one	449, 451 Cl pattern
331	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-naphthalen-2-ylmethyl)-piperazin-2-one	432, 434 Cl pattern
332	1-(4-Amino-quinazolin-7-ylmethyl)-4-isoquinolin-3-ylmethyl-piperazin-2-one	399
333	1-(4-Amino-quinazolin-7-ylmethyl)-4-[1-(3-chloro-phenyl)-pyrrolidin-3-yl]-piperazin-2-one	437, 439 Cl pattern
334	1-(4-Amino-quinazolin-7-ylmethyl)-4-(1,7-dichloro-isoquinolin-3-ylmethyl)-piperazin-2-one	467, 469 Cl pattern
335	4-(2-Amino-7-chloro-quinolin-3-ylmethyl)-1-(4-amino-quinazolin-7-ylmethyl)-piperazin-2-one	448, 450 Cl pattern
336	1-(4-Aminoquinazolin-7-ylmethyl)-4-(5-chloro-benzo[b]thiophene-2-ylmethyl)piperazin-2-one.	438, 440 Cl pattern
337	1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(4-chloro-phenylsulfanyl)-ethyl]-piperazin-2-one	428, 430 Cl pattern
338	1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(6-chloro-benzo[b]thiophen-	452, 454

	2-yl)-ethyl]-piperazin-2-one	Cl pattern
339	1-(4-Aminoquinazolin-7-ylmethyl)-4-[2-(4-chloro-phenoxy)-ethyl]-piperazine-2-one	412, 414 Cl pattern
340	2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-6-chloro-4H-benzo[1,4]thiazin-3-one	469, 471 Cl pattern
341	1-(4-Amino-quinazolin-7-ylmethyl)-4-(2,7-dichloro-quinolin-3-ylmethyl)-piperazin-2-one	467, 469 Cl ₂ pattern
342	2-[[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-4-chloro-phenyl]-methyl]-acrylic acid ethyl ester	480, 482 Cl pattern
343	2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-3-(4-chloro-phenyl)-acrylic acid ethyl ester	480, 482 Cl pattern
344	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-phenyl)-allyl]-piperazin-2-one	408, 410 Cl pattern
345	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-chloro-phenyl)-allyl]-piperazin-2-one	408, 410 Cl pattern
346	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-bromo-thiophen-2-yl)-allyl]-piperazin-2-one	458, 460 Br pattern
347	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-allyl]-piperazin-2-one	458, 460 Br pattern
348	3-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-7-fluoro-1H-quinolin-2-one	433
349	3-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-6-chloro-1H-quinoxalin-2-one	450, 452 Cl pattern
350	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1-methyl-1H-benzoimidazol-2-ylmethyl)-piperazin-2-one	436, 438 Cl pattern
351	2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-6-chloro-3H-quinazolin-4-one	492, 494 Cl pattern
352	1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-thiophen-2-yl-propyl)-piperazin-2-one	382
353	1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-quinolin-3-ylmethyl)-piperazin-2-one	432, 434 Cl pattern
354	3-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-5,7-dichloro-1H-quinolin-2-one	483, 485 Cl pattern
355	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6,7-dichloro-	472, 474

	benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	Cl ₂ pattern
356	3-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-5-chloro-1H-quinolin-2-one	449, 451 Cl pattern
357	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-[2,3']bithiophenyl-5-ylmethyl)-piperazin-2-one	470, 472 Cl pattern
358	4-(6-Amino-benzo[b]thiophen-2-ylmethyl)-1-(4-amino-quinazolin-7-ylmethyl)-piperazin-2-one	419
359	1-(4-Amino-quinazolin-7-ylmethyl)-4-(2-chloro-quinolin-6-ylmethyl)-piperazin-2-one	433, 435 Cl pattern
360	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-bromo-1H-benzoimidazol-2-ylmethyl)-piperazin-2-one	466, 468 Br pattern
361	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-nitro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	449
362	1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(3-chloro-phenyl)-thiophen-2-ylmethyl]-piperazin-2-one	464, 466 Cl pattern
363	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-3-methoxy-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	468, 470 Cl pattern
364	3-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-ylmethyl]-6-chloro-1H-quinolin-2-one	449, 451 Cl pattern
3653	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-trifluoromethyl-1H-benzoimidazol-2-ylmethyl)-piperazin-2-one	456
366	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-methyl-[2,2']bithiophenyl-5-ylmethyl)-piperazin-2-one	450
367	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-methyl-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	418
368	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-3,3'-dimethyl-[2,2']bithiophenyl-5-ylmethyl)-piperazin-2-one	498, 500 Cl pattern
369	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3,5-dibromo-4-methoxy-phenyl)-{1,2,4}oxadiazol-5-ylmethyl]-piperazin-2-one	602, 604, 606 Br ₂ pattern
370	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-methyl-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	418
371	1-(4-Amino-quinazolin-7-ylmethyl)-4-(4-methyl-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	418

372	1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	438, 440 Cl pattern
373	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-3'-methyl-[2,2']bithiophenyl-5-ylmethyl)-piperazin-2-one	484, 486 Cl pattern
374	1-(4-Amino-quinazolin-7-ylmethyl)-4-(1H-benzoimidazol-2-ylmethyl)-piperazin-2-one	388
375	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-bromo-[2,2']bithiophenyl-5-ylmethyl)-piperazin-2-one	514, 516 Br pattern
376	1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-oxazol-2-ylmethyl]-piperazin-2-one	473
377	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5,6-dichloro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	472, 474 Cl pattern
378	1-(4-Amino-quinazolin-7-ylmethyl)-4-(4,5-dichloro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	472, 474 Cl pattern
379	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-benzooxazol-2-ylmethyl)-piperazin-2-one	423, 425 Cl pattern
380	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-5-fluoro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	456, 458 Cl pattern
381	1-(4-Amino-quinazolin-7-ylmethyl)-4-(4-chloro-5-fluoro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	456, 458 Cl pattern
382	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-3-methyl-[2,2']bithiophenyl-5-ylmethyl)-piperazin-2-one	484, 486 Cl pattern
383	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-thieno[3,2-b]pyridin-2-ylmethyl)-piperazin-2-one	439, 441 Cl pattern
384	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5,6-dichloro-1H-benzoimidazol-2-ylmethyl)-piperazin-2-one	456
385	1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-benzooxazol-2-yl-benzyl)-piperazin-2-one	464
386	1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(4-chloro-phenyl)-thiophen-2-ylmethyl]-piperazin-2-one	464, 466 Cl pattern
387	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-methyl-1H-benzoimidazol-2-ylmethyl)-piperazin-2-one	402
388	1-(4-Amino-quinazolin-7-ylmethyl)-4-[2,2']bithiophenyl-5-ylmethyl-piperazin-2-one	435

389	1-(4-Amino-quinazolin-7-ylmethyl)-4-(4-fluoro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	422
390	1-(4-Aminoquinazolin-7-ylmethyl)-4-(6-fluoro-benzo[b]thiophene-2-ylmethyl)piperazin-2-one.	422
391	1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(1-methyl-5-trifluoro-methyl-1H-pyrazol-3-yl)-thiophen-2-ylmethyl]-piperazin-2-one	501
392	1-(4-Amino-quinazolin-7-ylmethyl)-4-(3,4-dimethyl-thieno[2,3-b]thiophen-2-ylmethyl)-piperazin-2-one	438
393	1-(4-Amino-quinazolin-7-ylmethyl)-4-(4-chloro-3-methyl-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	452, 454 Cl pattern
394	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-3-methyl-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	452, 454 Cl pattern
395	1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(2-methyl-5-trifluoromethyl-2H-pyrazol-3-yl)thiophen-2-ylmethyl] piperazin-2-one	502
396	1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(3-nitro-phenyl)-furan-2-ylmethyl]-piperazin-2-one	459
397	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-thieno[3,2-b]pyridin-6-ylmethyl)-piperazin-2-one	439, 441 Cl pattern
398	1-(4-Amino-quinazolin-7-ylmethyl)-4-[5-(4-methoxy-phenyl)-thiophen-2-ylmethyl]-piperazin-2-one	460
399	1-(4-Amino-quinazolin-7-ylmethyl)-4-(4-hydroxy-2-pyridin-2-yl-pyrimidin-5-ylmethyl)-piperazin-2-one	443
400	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-fluoro-phenoxy)-benzyl]-piperazin-2-one	458
401	1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(4-chloro-phenyl)-thiazol-4-ylmethyl]-piperazin-2-one	465, 467 Cl pattern
402	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-bromo-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	482, 484 Br pattern
403	1-(4-Amino-quinazolin-7-ylmethyl)-4-benzo[b]thiophen-2-ylmethyl-piperazin-2-one	404
404	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-ylmethyl)-piperazin-2-one	470, 472 Cl pattern
405	1-(4-Amino-quinazolin-7-ylmethyl)-4-(3,5-bis-trifluoromethyl-benzyl)-piperazin-2-one	488

406	1-(4-Amino-quinazolin-7-ylmethyl)-4-biphenyl-4-ylmethyl-piperazin-2-one	423 (M+)
407	1-(4-Amino-quinazolin-7-ylmethyl)-4-naphthalen-2-ylmethyl-piperazin-2-one	397 (M+)
408	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-benzo[b]thiophen-3-ylmethyl)-piperazin-2-one	438, 440 Cl pattern
409	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-thieno[2,3-b]pyridin-2-ylmethyl)-piperazin-2-one	438, 440Cl pattern

EXAMPLE 410. 1-(4-Aminoquinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-(E)-acryloyl]piperazin-2-one.

The title compound is prepared as described in EXAMPLE 123 using 1-(4-

5 aminoquinazoline-7-ylmethyl)piperazine-2-one bishydrochloride, EXAMPLE 72, in place of 4-(2-oxopiperazin-1-ylmethyl)benzamidine bistrifluoroacetate. ^1H NMR (d6-DMSO, 300 MHz) δ 9.77 (bs, 2H), 8.83 (s, 1H), 8.40 (dd, 1H), 7.68 (d, 1H), 7.65 (s, 1H), 7.58 (d, 2H), 7.15 (d, 2H), 4.80 (s, 2H), 4.33, 4.15 (m, 2H, rotamers), 3.70 (m, 2H), 3.49 (m, 2H). ESI MS, $[\text{M}+\text{H}]^+=456, 458$ (Br pattern).

10

The following compounds are prepared from the compound of Example 72 using the methods described above.

Example	Name	m/z [M+H]
411	1-(4-Amino-quinazolin-7-ylmethyl)-4-(4-chloro-thiophene-2-carbonyl)-piperazin-2-one	402, 404 Cl pattern
412	4-[3-(3-Amino-4-chloro-phenyl)-(E)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-piperazin-2-one	437, 439 Cl pattern
413	1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-chloro-1H-indole-6-carbonyl)-piperazin-2-one	435, 437 Cl pattern
414	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]piperazin-2-one	432, 434 Cl pattern
415	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-bromo-thiophen-2-yl)-(E)-acryloyl]-piperazin-2-one	472, 474 Br pattern
416	5-Chloro-thiophene-2-carboxylic acid {2-[4-(4-amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-2-oxo-ethyl}-amide	459, 461 Cl pattern
417	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-(E)-	428, 430

	acryloyl]-piperazin-2-one	Cl pattern
418	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-carbonyl)-piperazin-2-one	435, 437 Cl pattern
419	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(6-chloro-benzo[b]thiophen-2-yl)-(E)-acryloyl]-piperazin-2-one	478, 480 Cl pattern
420	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-(E)-acryloyl]-piperazin-2-one	472, 474 Br pattern
421	5-Chloro-thiophene-2-carboxylic acid {2-[4-(4-amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-1-methyl-2-oxo-ethyl}-amide	473, 475 Cl pattern
422	5-Chloro-thiophene-2-carboxylic acid {3-[4-(4-amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-3-oxo-propyl}-amide	473, 475 Cl pattern
423	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-phenoxy)-acetyl]-piperazin-2-one	426, 428 Cl pattern
424	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-2-methyl-phenoxy)-acetyl]-piperazin-2-one	440, 442 Cl pattern
425	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-carbonyl)-piperazin-2-one	484, 486 Cl pattern
426	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-propionyl]-piperazin-2-one	430, 432 Cl pattern
427	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-chloro-phenyl)-(E)-acryloyl]-piperazin-2-one	422, 424 Cl pattern
428	N-[2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-yl]-1-(5-chloro-thiophen-2-ylmethyl)-2-oxo-ethyl]-benzamide	428, 430 Cl pattern
429	N-[1-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carbonyl]-2-(5-chloro-thiophen-2-yl)-vinyl]-benzamide	549, 550 Cl pattern
430	N-[1-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carbonyl]-2-(5-chloro-thiophen-2-yl)-vinyl]-acetamide	485, 487 Cl pattern
431	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-phenyl)-(E)-acryloyl]-piperazin-2-one	422, 424 Cl pattern
432	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yl)-acetyl]-piperazin-2-one	415, 417 Cl pattern
433	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-carbonyl)-piperazin-2-one	451, 453 Cl pattern
434	2-[4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carbonyl]-	483, 485

	6-chloro-4H-benzo[1,4]thiazin-3-one	Cl pattern
435	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(6-chloro-benzo[b]thiophen-2-yl)-acetyl]-piperazin-2-one	466, 468 Cl pattern

EXAMPLE 436. 4-(4-Aminoquinazolin-7-ylmethyl)-3-oxopiperazine-1-carboxylic acid 4-chlorobenzylamide.

To a solution of 1-(4-aminoquinazoline-7-ylmethyl)piperazine-2-one (25 mg, 0.097 mmol), EXAMPLE 72, in 1 mL of DMF is added 4-chloro-benzyl isocyanate (22 mg, 0.13 mmol, prepared as described in EXAMPLE 37). After stirring 1 h at room temperature, the solution is concentrated. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 80% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are combined and lyophilized to provide the title compound (36 mg, 0.067 mmol) as a white solid. ¹H NMR (d6-DMSO, 300 MHz) δ 9.76 (bs, 2H), 8.83 (s, 1H), 8.38 (d, 1H), 7.64 (d, 1H), 7.60 (s, 1H), 7.34 (d, 2H), 7.31 (m, 1H), 7.26 (d, 2H), 4.75 (s, 2H), 4.22 (d, 2H), 4.08 (s, 2H), 3.60 (m, 2H), 3.35 (m, 2H). ESI MS, [M+H]⁺=425,427 (Cl pattern).

EXAMPLE 437. 4-(4-Aminoquinazolin-7-ylmethyl)-3-oxopiperazine-1-carboxylic acid (5-chlorothiophen-2-ylmethyl)amide.

To a solution of (5-chloro-thiophen-2-yl)-acetic acid (0.18 g, 1.04 mmol), prepared as described in EXAMPLE 27 in 6 mL of dry CH₂Cl₂ is added Et₃N (0.15 mL g, 1.04 mmol) and diphenylphosphoryl azide (0.24 mL, 1.04 mmol). The mixture is stirred at room temperature for 2.5 h, then heated at 50°C for 2 hours. To the solution is added 1-(4-aminoquinazoline-7-ylmethyl)piperazine-2-one (0.10 g, 0.41 mmol), EXAMPLE 72, and Et₃N (0.15 mL g, 1.04 mmol) and the mixture is heated at 50°C for 2 h, then stirred at room temperature for 16 hours. The resulting mixture is concentrated. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are combined and lyophilized to provide the title compound (10 mg, 0.02 mmol) as a white solid. ¹H NMR (d6-DMSO, 300 MHz) δ 9.69 (bs, 2H), 8.80 (s, 1H), 8.48 (d, 1H), 7.61 (d, 1H), 7.60 (s, 1H), 7.41 (t, 1H), 6.90 (d, 1H), 6.80 (d, 1H), 4.77 (d, 2H), 4.30 (d, 2H), 4.10 (s, 2H), 3.61 (m, 2H), 3.38 (m, 2H). ESI MS, [M+H]⁺=431,433 (Cl pattern).

EXAMPLE 438. 4-(4-Aminoquinazolin-7-ylmethyl)-3-oxopiperazine-1-carboxylic acid (5-chlorothiophen-2-yl)amide.

A mixture of 5-chloro-thiophene-2-carbonyl azide (55 mg, 0.29 mmol, prepared as described in EXAMPLE 38) and 1-(4-aminoquinazoline-7-ylmethyl)piperazine-2-one (50 mg, 0.20 mmol), EXAMPLE 72, in 3 mL of dry toluene is heated at 105°C for 1 hours. The resulting

mixture is concentrated in vacuo. The crude product is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 60% CH₃CN/H₂O (0.1% TFA) and the appropriate product fractions are combined and lyophilized to provide the title compound (35 mg, 0.02 mmol) as a white solid. ¹H NMR (DMSO-d₆, 300 MHz) δ 10.04 (s, 1H), 9.71 (bs, 2H), 8.81 (s, 1H), 8.38 (dd, 1H), 7.64 (d, 1H), 7.61 (s, 1H), 6.77 (d, 1H), 6.42 (d, 1H), 4.76 (s, 2H), 4.21 (s, 2H), 3.73 (m, 2H), 3.40 (m, 2H). ESI-MS, [M+H]⁺=417,419 (Cl pattern).

The following compounds are prepared from the compound of Example 72 using the methods described above.

Example	Name	m/z [M+H]
439	4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carboxylic acid (4-chloro-thiophen-2-yl)-amide	417, 419 Cl pattern
440	4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carboxylic acid (5-bromo-thiophen-2-yl)-amide	461, 463 Br pattern
441	4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carboxylic acid (3-amino-4-chloro-phenyl)-amide	426, 428 Cl pattern
442	4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carboxylic acid (4-bromo-phenyl)-amide	455, 457 Br pattern
443	4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide	411, 413 Cl pattern
444	4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carboxylic acid (4-methoxy-phenyl)-amide	407
445	4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carboxylic acid (3,4-dichloro-phenyl)-amide	445, 447 Cl ₂ pattern

10 EXAMPLE 446. 4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carboxylic acid 5-chloro-thiophen-2-ylmethyl ester.

To a solution of 5-chloro-2-thiophene-methanol (0.10 g, 0.67 mmol, prepared by NaBH₄ reduction of 5-chloro-2-thiophene-carboxaldehyde) in 6 mL of CH₂Cl₂ is added 1,1'-carbonyldiimidazole (0.11 g, 0.67 mmol). The mixture is stirred at room temperature for 3 hours. Then 1-(4-aminoquinazoline-7-ylmethyl)piperazine-2-one (0.17 g, 0.67 mmol, EXAMPLE 72) and a catalytic amount of DMAP is added to the solution and the resulting mixture is heated at 35°C for 18 hours. The mixture is dissolved in water/MeOH and the crude product is purified by RP-HPLC eluting in a gradient of 10% CH₃CN/H₂O (0.1% TFA) to 100%

CH₃CN. The appropriate fractions are combined and lyophilized to provide the title compound as a white solid. ESI MS, [M+H]⁺=432,434 (Cl pattern).

The following compounds are prepared from the compound of Example 72 using the

5 methods described above.

Example	Name	m/z [M+H]
447	4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazin-1-carboxylic acid 6-chloro-benzooxazol -2-ylmethyl ester	467, 469 Cl pattern
448	4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-piperazine-1-carboxylic acid 1-(3-chloro-phenyl)-pyrrolidin-3-yl ester	481, 483 Cl pattern

EXAMPLE 449. 1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-3-(S)-methyl-piperazin-2-one.

To a solution of 1-(4-amino-quinazoline-7-ylmethyl)-3-methyl-piperazine-2-one,

EXAMPLE 80, (0.06g, 0.2mmol) in 2 mL of DMF is added 3-bromomethyl-7-chloroisoquinoline,

10 EXAMPLE 11, 0.052g, 0.20mmol), and K₂CO₃ (0.08 g, 0.06 mmol). After 16 h, the reaction mixture is concentrated to dryness. The crude product is purified by RP-HPLC eluting with a gradient of 5%CH₃CN/H₂O (0.1% TFA) to 50%CH₃CN/H₂O (0.1% TFA). The product fractions are lyophilized to give the title compound as a tris(trifluoroacetic acid salt (0.06g, 0.08 mmol) as a white solid. ¹H NMR (d6-DMSO, 300 MHz) δ 9.79 (bs, 2H), 9.40 (s, 1H), 8.73 (s, 1H), 8.33 (d, 1H), 8.25 (s, 1H), 8.06 (s, 1H), 8.00 (d, 1H), 7.79 (d, 1H), 7.60 (m, 2H), 4.80 (AB, 2H), 4.72 (AB, 2H), 4.28 (m, 1H), 3.54 (m, 4H), 1.96 (d, 3H). MS (ion spray) 447, 449, (Cl pattern). Elemental analysis C₂₈H₂₅ClF₆N₆O₆·3CF₃CO₂H·0.28H₂O, cal C=45.38%, H=3.35%, N=10.58%; found C=45.38, H=3.35%, N=10.63%.

20 EXAMPLE 450. 4-(4-Amino-quinazolin-7-ylmethyl)- 4-(3-chloro-1H-indol-6-ylmethyl)-3-(S)-methyl-piperazin-2-one.

The title compound is prepared as described in EXAMPLE 274 using 1-(4-amino-quinazoline-7-ylmethyl)-3-methyl-piperazine-2-one, EXAMPLE 80. ¹H NMR (DMSO-d₆, 300 MHz) δ 9.79 (bs, 2H), 8.82 (s, 1H), 8.39 (d, 1H), 7.61 (m, 3H), 7.57 (d, 1H), 7.52 (d, 1H), 7.49 (d, 1H), 7.20 (d, 1H), 7.10 (d, 1H), 4.75 (AB, 2H), 4.57 (m, 1H), 4.23 (m, 1H), 3.97 (m, 1H), 3.50 (m, 3H), 1.65 (d, 3H). ESI MS, [M+H]⁺= 435,437 (Cl pattern). Anal. (C₂₃H₂₃CIN₆O₂·1.5TFA·0.25H₂O) C, H, N.

The following compounds are prepared from the compound of Example 80 using the

30 methods described above.

Example	Name	m/z [M+H]
451	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-allyl]-3-(S)-methyl-piperazin-2-one	428, 430 Cl pattern
452	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(6-chloro-benzo[b]thiophen-2-yl)-allyl]-3-(S)-methyl-piperazin-2-one	478, 480 Cl pattern
453	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-propyl]-3-(S)-methyl-piperazin-2-one	429, 431 Cl pattern
454	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-3-(S)-methyl-piperazin-2-one	435, 437 Cl pattern
455	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-but-2-enyl]-3-(S)-methyl-piperazin-2-one	442, 444 Cl pattern
456	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-ylmethyl)-3-(S)-methyl-piperazin-2-one	483 (M+) (EI)
457	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-benzimidazol-2-ylmethyl)-3-(S)-methyl-piperazin-2-one	536, 538 Cl pattern
458	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-(S)-methyl-piperazin-2-one	428, 430 Cl pattern
459	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-naphthalen-2-ylmethyl)-3-(S)-methyl-piperazin-2-one	446, 448 Cl pattern
460	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-thieno[2,3-b]pyridin-2-ylmethyl)-3-(S)-methyl-piperazin-2-one	453, 455 Cl pattern
461	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-3-(S)-methyl-piperazin-2-one	452, 454 Cl pattern
462	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-benzo[b]thiophen-2-ylmethyl)-3-(S)-methyl-piperazin-2-one	452, 454 Cl pattern
463	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-benzo[b]thiophen-2-ylmethyl)-3-(R)-methyl-piperazin-2-one	452, 454 Cl pattern
464	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-3-(R)-methyl-piperazin-2-one	452, 454 Cl pattern

EXAMPLE 465 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-acryloyl]-3-(S)-methyl-piperazin-2-one.

The title compound is prepared as described in EXAMPLE 123, using 1-(4-amino-5-quinazoline-7-ylmethyl)-3-methyl-piperazine-2-one, EXAMPLE 80, and 3-(4-chloro-thiophen-2-

yl)-(E)-acrylic acid, EXAMPLE 26. ^1H NMR (d6-DMSO, 300 MHz) δ 9.74 (bs, 2H), 8.82 (s, 1H), 8.40 (d, 1H), 7.62 (m, 5H), 7.05 (d, 1H), 4.92 (m, 1H), 4.80 (m, 2H), 4.73 (m, 1H), 4.50 (m, 1H), 3.40 (m, 2H), 1.42 (m, 3H). ESI MS, $[\text{M}+\text{H}]^+ = 442, 444$ (Cl pattern).

5 The following compounds are prepared from the compound of Example 80 using the methods described above.

Example	Name	m/z [M+H]
466	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-3-yloxy)-acetyl]-3-(S)-methyl-piperazin-2-one	446, 448 Cl pattern
467	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methyl-piperazin-2-one	446, 448 Cl pattern
468	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-bromo-thiophen-2-yl)-acryloyl]-3-(S)-methyl-piperazin-2-one	486, 488 Br pattern
469	1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-chloro-1H-indole-6-carbonyl)-3-(S)-methyl-piperazin-2-one	449, 451 Cl pattern
470	1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinoline-3-carbonyl)-3-(S)-methyl-piperazin-2-one	461, 463 Cl pattern
471	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methyl-piperazin-2-one	446, 448 Cl pattern
472	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3-(S)-methyl-piperazin-2-one	486, 488 Br pattern
473	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-phenoxy)-acetyl]-3-(S)-methyl-piperazin-2-one	440, 442 Cl pattern
474	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5'-chloro-[2,2']bithiophenyl-5-carbonyl)-3-(S)-methyl-piperazin-2-one	498, 500 Cl pattern
475	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-but-2-enoyl]-3-(S)-methyl-piperazin-2-one	456, 458 Cl pattern
476	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-carbonyl)-3-(S)-methyl-piperazin-2-one	466, 468 Cl pattern
477	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(S)-methyl-piperazin-2-one	442, 444 Cl pattern

EXAMPLE 478. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-propyl]-3-(S)-ethyl-piperazin-2-one.

10 The title compound is prepared as described in EXAMPLE 278 using 1-(4-aminoquinazoline-7-ylmethyl)-3-ethyl-piperazine-2-one, EXAMPLE 77 and 3-(5-chloro-

thiophen-2-yl)-propionaldehyde, EXAMPLE 28. ^1H NMR (d6-DMSO + 1 drop TFA, 300 MHz) δ 9.80 (bs, 2H), 8.79 (s, 1H), 8.32 (d, 1H), 7.58 (m, 2H), 6.88 (d, 1H), 6.70 (d, 1H), 4.72 (AB, 2H), 4.00 (m, 1H), 3.72 (m, 1H), 3.48 (m, 2H), 3.23 (m, 3H), 2.72 (m, 2H), 1.96 (m, 4H), 0.98 (m, 3H). MS (ion spray), m/z, (M+H) = 444, 446 (Cl pattern).

5

The following compounds are prepared from the compound of Example 77 using the methods described above.

Example	Name	m/z [M+H]
479	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-allyl]-3-(S)-ethyl-piperazin-2-one	442, 444 Cl pattern
480	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-but-2-enyl]-3-(S)-ethyl-piperazin-2-one	456, 458 Cl pattern
481	1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-3-(S)-ethyl-piperazin-2-one	461, 463 Cl pattern
482	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-(S)-ethyl-piperazin-2-one	442, 444 Cl pattern
483	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-naphthalen-2-ylmethyl)-3-(S)-ethyl-piperazin-2-one	460, 462 Cl pattern
484	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-3-(S)-ethyl-piperazin-2-one	466, 468 Cl pattern
485	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-thieno[2,3-b]pyridin-2-ylmethyl)-3-(S)-ethyl-piperazin-2-one	467, 469 Cl pattern

EXAMPLE 486. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(S)-ethyl-piperazin-2-one.

10

The title compound is prepared as described in EXAMPLE 123, using 1-(4-aminoquinazoline-7-ylmethyl)-3-ethyl-piperazine-2-one, EXAMPLE 77 and 3-(5-chloro-thiophen-2-yl)-(E)-acrylic acid, EXAMPLE 25. ^1H NMR (d6-DMSO + 1 drop TFA, 300 MHz) δ 9.78 (bs, 2H), 8.79 (s, 1H), 8.37 (d, 1H), 7.65 (m, 2H), 7.50 (s, 1H), 7.41 (m, 1H), 7.11 (d, 1H), 6.98 (d, 1H), 4.88 (m, 2H), 4.60 (m, 1H), 4.31 (m, 1H), 3.52 (m, 1H), 3.30 (m, 2H), 1.96 (m, 2H), 0.88 (m, 3H). MS (ion spray), m/z, (M+H) = 456, 458 (Cl pattern). Elemental analysis, cal C₂₂H₂₂ClN₅O₂S·1.5C₂HF₃O₂ %C=47.89, %H=3.78, %N=11.17; found %C=47.34, %H=4.00, %N=11.12.

20

The following compounds are prepared from the compound of Example 77 using the methods described above.

Example	Name	m/z [M+H]
487	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-thiophen-2-yloxy)-acetyl]-3-ethyl-piperazin-2-one	460, 462 Cl pattern
488	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-3-yloxy)-acetyl]-3-ethyl-piperazin-2-one	460, 462 Cl pattern
489	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-3-yl)-acryloyl]-3-ethyl-piperazin-2-one	456, 458 Cl pattern
490	2-(2-[4-(4-Amino-quinazolin-7-ylmethyl)-(S)-2-ethyl-3-oxo-piperazin-1-yl]-2-oxo-ethoxy)-5-chloro-thiophen-3-yl)-acetamide	517, 519 Cl pattern
491	(2-[2-[4-(4-Amino-quinazolin-7-ylmethyl)-(S)-2-ethyl-3-oxo-piperazin-1-yl]-2-oxo-ethoxy)-5-chloro-thiophen-3-yl)-acetic acid	518, 520 Cl pattern
492	1-(4-Amino-quinazolin-7-ylmethyl)-4-(2,3-dichloro-benzo[b]thiophene-6-carbonyl)-(S)-3-ethyl-piperazin-2-one	514, 516, 518 Cl ₂ pattern
493	1-(4-Amino-quinazolin-7-ylmethyl)-4-(2-chloro-benzo[b]thiophene-6-carbonyl)-(S)-3-ethyl-piperazin-2-one	480, 482 Cl pattern
494	(2-[2-[4-(4-Amino-quinazolin-7-ylmethyl)-(S)-2-ethyl-3-oxo-piperazin-1-yl]-2-oxo-ethoxy)-5-chloro-thiophen-3-yl)-acetic acid ethyl ester	546, 548 Cl pattern
495	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3,5-dichloro-thiophen-2-yloxy)-acetyl]-3-ethyl-piperazin-2-one	494, 496 Cl pattern
496	(2-[2-[4-(4-Amino-quinazolin-7-ylmethyl)-(S)-2-ethyl-3-oxo-piperazin-1-yl]-2-oxo-ethoxy)-5-chloro-thiophen-3-yl)-acetic acid methyl ester	532, 534 Cl pattern
497	1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-chloro-1H-indole-6-carbonyl)-(3S)-ethyl-piperazin-2-one	463, 465
498	1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinoline-3-carbonyl)-3-(S)-ethyl-piperazin-2-one	475, 477 Cl pattern
499	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-ethyl-piperazin-2-one	460, 462 Cl pattern
500	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-bromo-thiophen-2-yl)-acryloyl]-3-(S)-ethyl-piperazin-2-one	500, 502 Br pattern

501	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-acryloyl]-3-(S)-ethyl-piperazin-2-one	456, 458 Cl pattern
502	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3-(S)-ethyl-piperazin-2-one	500, 502 Br pattern
503	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-propionyl]-3-(S)-ethyl-piperazin-2-one	458, 460 Cl pattern
504	1-(4-Amino-quinazolin-7-ylmethyl)-4-[1-(4-chloro-phenyl)-1H-pyrrole-2-carbonyl]-3-(S)-ethyl-piperazin-2-one	489, 491 Cl pattern
505	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-phenylsulfanyl)-acetyl]-3-(S)-ethyl-piperazin-2-one	470, 472 Cl pattern
506	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-but-2-enoyl]-3-(S)-ethyl-piperazin-2-one	470, 472 Cl pattern
507	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-phenoxy)-acetyl]-3-(S)-ethyl-piperazin-2-one	454, 456 Cl pattern
508	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-phenyl)-acryloyl]-3-(S)-ethyl-piperazin-2-one	450, 452 Cl pattern
509	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indole-2-carbonyl)-3-(S)-ethyl-piperazin-2-one	463, 465 Cl pattern
510	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-phenyl)-propionyl]-3-(S)-ethyl-piperazin-2-one	452, 454 Cl pattern
511	1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-ethyl-4-[3-(4-methoxy-phenyl)-propionyl]-piperazin-2-one	448
512	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-carbonyl)-3-(S)-ethyl-piperazin-2-one	480, 482 Cl pattern

EXAMPLE 513. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-propyl-piperazin-2-one.

The title compound is prepared as described in EXAMPLE 123, using 1-(4-aminoquinazoline-7-ylmethyl)-3-propyl-piperazine-2-one, EXAMPLE 78 and 5-chloro-2-

5 thienyloxyacetic acid, EXAMPLE 24. ^1H NMR (d6-DMSO, 300 MHz) δ 9.78 (bs, 2H), 8.81 (s, 1H), 8.35 (d, 1H), 7.60 (m, 2H), 7.51 (s, 1H), 6.69 (m, 1H), 6.21 (d, 1H), 4.91 (AB, 2H), 4.72 (m, 2H), 3.84 (m, 1H), 3.52 (m, 2H), 3.23 (m, 1H), 1.80 (m, 2H), 1.24 (m, 2H), 0.82 (m, 3H). MS (ion spray), m/z, 474, 476, (M+H) (Cl pattern). Elemental analysis, cal $\text{C}_{22}\text{H}_{22}\text{ClN}_5\text{O}_2\text{S}\cdot\text{C}_2\text{HF}_3\text{O}_2\cdot1.15\text{H}_2\text{O}$ %C=47.31, %H=4.52, %N=11.50; found %C=47.39,
10 %H=4.140, %N=11.19.

EXAMPLE 514. 4-[3-(6-Amino-pyridin-3-yl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-3-(S)-propyl-piperazin-2-one.

The title compound is prepared as described in EXAMPLE 123, using 1-(4-aminoquinazoline-7-ylmethyl)-3-propyl-piperazine-2-one, EXAMPLE 78 and 3-(6-amino-pyridin-3-yl)-acrylic acid, EXAMPLE 36. ^1H NMR (d6-DMSO, 300 MHz) δ 9.73 (bs, 2H), 8.81 (s, 1H), 8.36 (m, 2H), 8.22 (m, 3H), 7.62 (d, 1H), 7.52 (m, 1H), 7.39 (m, 1H), 7.21 (m, 1H), 6.91 (d, 1H), 5.00 (m, 1H), 4.78 (m, 1H), 4.60 (m, 2H), 4.34 (m, 1H), 3.30 (m, 2H), 1.87 (m, 2H), 1.24 (m, 2H), 0.90 (m, 3H). MS (ion spray), m/z, 446, 448 (M+H), (Cl pattern).

10 The following compounds are prepared from the compound of Example 78 using the methods described above.

Example	Name	m/z [M+H]
515	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(2,5-dichloro-thiophen-3-yloxy)-acetyl]-3-(S)-propyl-piperazin-2-one	508, 509, 511, Cl ₂ pattern
516	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-propyl-piperazin-2-one	474, 476 Cl pattern
517	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3-(S)-propyl-piperazin-2-one	514, 516 Br pattern
518	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-acryloyl]-3-(S)-propyl-piperazin-2-one	470, 472 Cl pattern
519	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-chloro-phenoxy)-acetyl]-3-(S)-propyl-piperazin-2-one	468, 470 Cl pattern
520	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-3-yloxy)-acetyl]-3-(S)-propyl-piperazin-2-one	474, 476 Cl pattern
521	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-chloro-5-methoxy-phenoxy)-acetyl]-3-(S)-propyl-piperazin-2-one	498, 500 Cl pattern
522	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-3-yl)-acryloyl]-3-(S)-propyl-piperazin-2-one	470, 472 Cl pattern
523	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(S)-propyl-piperazin-2-one	470, 472 Cl pattern

EXAMPLE 524. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-(S)-methoxymethyl-piperazin-2-one.

The title compound is prepared as described in EXAMPLE 278 using 1-(4-amino-quinazoline-7-ylmethyl)-3-methoxymethyl-piperazine-2-one, EXAMPLE 75 and 2-(3-bromo-(E)-

propenyl)-5-chloro-thiophene EXAMPLE 17. ^1H NMR (d6-DMSO, 300 MHz) δ 9.74 (bs, 2H), 8.80 (s, 1H), 8.38 (d, 1H), 7.69 (m, 2H), 7.02 (dd, 1H), 6.84 (d, 1H), 6.02 (m, 1H), 4.76 (AB, 2H), 3.86 (m, 4H), 3.30 (s, 3H), 3.23 (m, 2H), 3.02 (m, 2H). MS (ion spray), m/z, 458, 460, (M+H) (Cl pattern). Elemental analysis, cal $\text{C}_{22}\text{H}_{24}\text{ClN}_5\text{O}_2\text{S} \cdot 2\text{C}_2\text{HF}_3\text{O}_2 \cdot 1.45\text{H}_2\text{O}$ %C=43.85, %H=4.09, %N=9.83; found %C=43.92, %H=3.61, %N=9.63.

The following compounds are prepared from the compound of Example 75 using the methods described above.

Example	Name	m/z [M+H]
525	1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-chloro-1H-indol-6-ylmethyl)-3-(S)-methoxymethyl-piperazin-2-one	465, 467
526	1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yloxy)-ethyl]-3-(S)-methoxymethyl-piperazin-2-one	446, 448 Cl pattern
527	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-3-(S)-methoxymethyl-piperazin-2-one	446, 448 Cl pattern
528	1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-3-(R)-methoxymethyl-piperazin-2-one	477, 479 Cl pattern
529	1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-3-(S)-methoxymethyl-piperazin-2-one	477, 479 Cl pattern
530	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-naphthalen-2-ylmethyl)-3-(S)-methoxymethyl-piperazin-2-one	476, 478 Cl pattern
531	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-3-(S)-methoxymethyl-piperazin-2-one	482, 484 Cl pattern

EXAMPLE 532. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one.

To a solution of 4-(4-amino-quinazoline-7-ylmethyl)-2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester, EXAMPLE 75, (0.69g, 2.29mmol) in 9mL of DMF is added N,N-diisopropylethyl amine (0.89g, 6.87mmol), TBTU (0.76g, 2.36mmol), and 5-chloro-2-thienyloxyacetic acid, EXAMPLE 24, (0.40g, 2.08mmol). The solution is stirred for 16 hours. After this time the solution is concentrated. The crude material is purified by RP-HPLC eluting with a gradient of 10%CH₃CN/H₂O (0.1%TFA) to 80%CH₃CN/H₂O (0.1%TFA). The product fractions are lyophilized to give the product as a white solid (1.0g, 1.57mmol). ^1H NMR (d6-DMSO, 300MHz) δ 9.70 (bs, 2H), 8.78 (s, 1H), 8.29 (m, 1H), 7.55 (m, 2H), 6.72 (m, 1H), 6.22 (m, 1H), 4.80 (m, 4H), 3.78 (m, 4H), 3.59 (m, 3H), 3.31 and 3.2 (s, 3H rotational isomers). MS (ion

spray) M+H=476. Elemental Analysis: C₂₁H₂₂CIN₅O₄S·1.4CF₃CO₂H cal: C=45.03%, H=3.68%, N=11.04%; found C=44.98%, H=3.71%, N=11.02%.

EXAMPLE 533. 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-carbonyl)-

5 3-(S)-methoxymethyl-piperazin-2-one.

To a solution of 4-(4-amino-quinazoline-7-ylmethyl)-2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid benzyl ester, EXAMPLE 75, (20 mg, 0.066 mmol) in 1.5 mL of DMF is added TBTU (923.4 mg, 0.073 mmol), diisopropylethylamine (0.013 ml, 0.073 mmol) and 6-chloro-1H-benzoimidazole-2-carboxylic acid (prepared from literature in Eur.J.med.Chem. 1993, 28, 71) (14.3 mg, 0.073 mmol). The resulting mixture is left to stir at room temperature overnight. The crude mixture is directly purified by reverse phase HPLC (10-70% ACN/H₂O). The product (30.1 mg, 55%) is isolated as a white powder. C₂₃H₂₂CIN₇O₃ MS m/z: 480, 481. Anal. cald. for C₂₃H₂₂CIN₇O₃·2C₂HF₃O₂: C, 45.81; H, 3.42; N, 13.85. Found C, 45.19; H, 3.59; N, 13.76.

15 The following compounds are prepared from the compound of Example 75 using the methods described above.

Example	Name	m/z [M+H]
534	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-thiophen-2-yloxy)-acetyl]-3-(S)- methoxymethyl-piperazin-2-one	476, 478 Cl pattern
535	4-[3-(4-Amino-phenyl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-3-(S)-methoxymethyl-piperazin-2-one	447
536	1-(4-Amino-quinazolin-7-ylmethyl)-4-(3-3H-imidazol-4-yl-acryloyl)-3-(S)-methoxymethyl-piperazin-2-one	
537	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(2,5-dichloro-thiophen-3-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	510, 512, Cl ₂ pattern
538	(1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-1H-benzoimidazole-2-carbonyl)-3-(S)-methoxymethyl-piperazin-2-one	480, 482 Cl pattern
539	1-(4-Amino-quinazolin-7-ylmethyl)-4-(5-chloro-thiophene-2-carbonyl)-3-(S)-methoxymethyl-piperazin-2-one	446, 448 Cl pattern
540	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-bromo-furan-2-yl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one	500, 502 Br pattern
541	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-phenyl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one	510, 512 Br pattern
542	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-phenyl)-acryloyl]-	466, 468

	3-(S)-methoxymethyl-piperazin-2-one	Cl pattern
543	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-bromo-phenyl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one	576, 578 Br pattern
544	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(3-chloro-phenyl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one	466, 468 Cl pattern
545	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-bromo-thiophen-2-yl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one	576, 578 Br pattern
546	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-3-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	476, 478 Cl pattern
547	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-pyridin-3-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	471, 473 Cl pattern
548	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(6-chloro-pyridin-2-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	471, 473 Cl pattern
549	4-[3-(6-Amino-pyridin-3-yl)-acryloyl]-1-(4-amino-quinazolin-7-ylmethyl)-3-(S)-methoxymethyl-piperazin-2-one	448
550	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-chloro-5-methoxy-phenoxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	500, 502 Cl pattern
551	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-3-yl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one	472, 474 Cl pattern
552	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(2,5-dichloro-phenoxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	504, 506, 508 Cl ₂ pattern
553	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-fluoro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	460
554	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-fluoro-phenoxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	453
555	1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(3-chloro-phenoxy)-propionyl]-3-(S)-methoxymethyl-piperazin-2-one	484, 486 Cl pattern
556	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(6-chloro-pyridin-3-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	471, 473 Cl pattern
557	1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-methoxymethyl-4-[(4-trifluoromethylsulfanyl-phenoxy)-acetyl]-piperazin-2-one	536
558	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-chloro-phenylamino)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	469, 471 Cl pattern

559	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-phenylamino)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	469, 471 Cl pattern
560	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-chloro-phenoxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	471, 473 Cl pattern
561	(2-{2-[4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazin-1-yl]-2-oxo-ethoxy}-5-chloro-thiophen-3-yl)-acetic acid	534, 536 Cl pattern
562	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-ylsulfanyl)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	492, 494 Cl pattern
563	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(6-chloro-pyridin-3-ylamino)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	470, 472 Cl pattern
564	2-(2-{2-[4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazin-1-yl]-2-oxo-ethoxy}-5-chloro-thiophen-3-yl)-acetic acid ethyl ester	533, 535 Cl pattern
565	1-(4-Amino-quinazolin-7-ylmethyl)-4-(2-chloro-benzo[b]thiophene-6-carbonyl)-3-(S)-methoxymethyl-piperazin-2-one	496, 498 Cl pattern
566	1-(4-Amino-quinazolin-7-ylmethyl)-4-(2,3-dichloro-benzo[b]thiophene-6-carbonyl)-3-(S)-methoxymethyl-piperazin-2-one	530, 532, 534 Cl ₂ pattern
567	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3,5-dichloro-thiophen-2-yloxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	510, 512, 514 Cl ₂ pattern
568	(2-{2-[4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazin-1-yl]-2-oxo-ethoxy}-5-chloro-thiophen-3-yl)-acetic acid methyl ester	548, 550 Cl pattern
569	(2-{2-[4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazin-1-yl]-2-oxo-ethoxy}-5-chloro-thiophen-3-yl)-acetic acid ethyl ester	562, 564 Cl pattern
570	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(2-chloro-pyridin-3-ylamino)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	470, 472 Cl pattern
571	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(2,3-dichloro-phenoxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	504, 506, 508 Cl ₂ pattern
572	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-fluoro-phenoxy)-acetyl]-3-	454

	(S)-methoxymethyl-piperazin-2-one	
573	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-2-methyl-phenoxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	484, 486 Cl pattern
574	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(2,4-dichloro-phenoxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	504, 506, 508 Cl ₂ pattern
575	1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinoline-3-carbonyl)-3-(S)-methoxymethyl-piperazin-2-one	491, 493 Cl pattern
576	(1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one	516, 518 Br pattern
577	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-chloro-thiophen-2-yl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one	472, 474 Cl pattern
578	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(R)-methoxymethyl-piperazin-2-one	472, 474 Cl pattern
579	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(S)-methoxymethyl-piperazin-2-one	472, 474 Cl pattern
580	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-carbonyl)-3-(S)-methoxymethyl-piperazin-2-one	496, 498 Cl pattern
581	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-phenoxy)-acetyl]-3-(S)-methoxymethyl-piperazin-2-one	470, 472 Cl pattern

EXAMPLE 582. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(6-chloro-pyridin-3-yloxy)-acetyl]-3-(S)-ethoxymethyl-piperazin-2-one.

The title compound is prepared as described in EXAMPLE 123, using 1-(4-aminoquinazoline-7-ylmethyl)-3-ethoxymethyl-piperazine-2-one, EXAMPLE 79 and, (6-chloro-pyridin-3-yloxy)-acetic acid, prepared similarly to the procedure described in EXAMPLE 29. ¹H NMR (d6-DMSO, 300 MHz) δ 9.73 (bs, 2H), 8.81 (s, 1H), 8.37 (m, 1H), 8.10 (m, 1H), 7.61 (m, 2H), 7.40 (m, 2H), 4.98 (m, 2H), 4.65 (m, 2H), 4.50 (m, 1H), 3.91 (m, 1H), 3.75 (m, 1H), 3.59 (m, 2H), 3.31 (m, 2H), 1.07 (m, 3H). MS (ion spray), m/z, 485, 487 (M+H), (Cl pattern).

10 The following compounds are prepared from the compound of Example 79 using the methods described above.

Example	Name	m/z [M+H]
583	1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-ethoxymethyl-4-[(3-fluoro-phenoxy)-acetyl]-piperazin-2-one	454

584	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(S)-ethoxymethyl-piperazin-2-one	486, 488 Cl pattern
585	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(2-chloro-pyridin-3-ylamino)-acetyl]-3-(S)-ethoxymethyl-piperazin-2-one	484, 486 Cl pattern
586	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(6-chloro-pyridin-3-ylamino)-acetyl]-3-(S)-ethoxymethyl-piperazin-2-one	484, 486 Cl pattern
587	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-ethoxymethyl-piperazin-2-one	490, 492 Cl pattern

The following compounds are prepared from the compounds of Examples 81-85 using the methods described above.

Example	Name	m/z [M+H]
588	1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-benzyl-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-piperazin-2-one	518, 520 Cl pattern
589	1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-benzyl-4-(6-chloro-benzo[b]thio-phene-2-carbonyl)-piperazin-2-one	542, 544 Cl pattern
590	1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-benzyl-4-[3-(5-chloro-thiophen-2-yl)-allyl]-piperazin-2-one	504, 506 Cl pattern
591	1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-benzyl-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-piperazin-2-one	528, 530 Cl pattern
592	1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-benzyl-4-[(4-chlorophenoxy)-acetyl]-piperazin-2-one	516, 518 Cl pattern
593	1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-benzyl-4-(6-chloro-naphthalen-2-ylmethyl)-piperazin-2-one	522, 524 Cl pattern
594	1-(4-Amino-quinazolin-7-ylmethyl)-3-(S)-benzyl-4-[3-(5-chloro-thiophen-2-yl)-propyl]-piperazin-2-one	506, 508 Cl pattern
595	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-((R)-1-methoxy-ethyl)-piperazin-2-one	490, 492 Cl pattern
596	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-(S)-((R)-1-methoxy-ethyl)-piperazin-2-one	472, 474 Cl pattern
597	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(S)-((R)-1-methoxy-ethyl)-piperazin-2-one	486, 488 Cl pattern
598	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3-(S)-((R)-1-methoxy-ethyl)-piperazin-2-one	530, 532 Br pattern
599	1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-	491, 493

	ylmethyl)-3-(S)-((R)-1-methoxy-ethyl)-piperazin-2-one	Cl pattern
600	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-3-(S)-isopropyl-piperazin-2-one	480, 482 Cl, pattern
601	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-3,3-dimethyl-piperazin-2-one	466, 468 Cl pattern
602	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,3-dimethyl-piperazin-2-one	442, 444 Cl pattern
603	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3,3-dimethyl-piperazin-2-one	456, 458 Cl pattern
604	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-carbonyl)-3,3-dimethyl-piperazin-2-one	480, 482 Cl pattern
605	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-(S)-(2-methoxy-ethyl)-piperazin-2-one	490, 492 Cl pattern
606	4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-(2-methoxy-ethyl)-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide	469, 471 Cl pattern
607	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-3-yloxy)-acetyl]-3-(S)-(2-methoxy-ethyl)-piperazin-2-one	490, 492 Cl pattern
608	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-carbonyl)-3-(S)-(2-methoxy-ethyl)-piperazin-2-one	510, 512 Cl pattern

EXAMPLE 609. 1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-naphthalen-2-ylmethyl)-3-(S)-methoxymethyl-6-(S)-methyl-piperazin-2-one.

The title compound is prepared as described in EXAMPLE 268, using 1-(4-amino-quinazoline-7-ylmethyl)-3-methoxymethyl-6-methyl-piperazine-2-one, EXAMPLE 87, and 2-bromomethyl-6-chloronaphthalene, EXAMPLE 12. ^1H NMR (CDCl_3 , 300 MHz) δ 8.59 (s, 1H), 7.79 (d, 1H), 7.70-7.12 (m, 3H), 7.68-7.67 (m, 2H), 7.55 (d, 1H), 7.39 (d, 1H), 4.78 (d, 2H), 3.98 (d, 2H), 3.44 (s, 3H), 3.38 (t, 1H), 2.64 (m, 2H), 1.26 (d, 3H). MS (ISP) 490, 492, ($\text{M}+\text{H}$), Cl pattern.

10 The following materials are prepared from starting materials obtained as described in Example 87 using the methods described above.

Example	Name	m/z [$\text{M}+\text{H}$]
610	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-propyl]-3-(S)-ethyl-6-methyl-piperazin-2-one	458, 460 Cl pattern

611	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-naphthalen-2-ylmethyl)-3-(S)-methoxymethyl-6-(R)-methyl-piperazin-2-one	490, 492 Cl pattern
612	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-(S)-methoxymethyl-6-methyl-piperazin-2-one	472, 474 Cl pattern
613	(1-(4-Amino-quinazolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-3-(S)-methoxymethyl-6-methyl-piperazin-2-one	490, 492 Cl pattern
614	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3-(S)-6-dimethyl-piperazin-2-one	491, 493 Cl pattern
615	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-naphthalen-2-ylmethyl)-6-methyl-piperazin-2-one	442, 446 Cl pattern
616	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-6-methyl-piperazin-2-one	428, 430 Cl pattern

EXAMPLE 617. 1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3(S)-methoxymethyl-6-methyl-piperazin-2-one.

The title compound is prepared as described in EXAMPLE 123 using 1-(4-amino-quinazoline-7-ylmethyl)-3-methoxymethyl-6-methyl-piperazine-2-one, EXAMPLE 87, and 5-chloro-2-thienyloxyacetic acid, EXAMPLE 24. ^1H NMR (CD_3OD 300 MHz) δ 8.68 (s, 1H), 8.27 (d, 1H), 7.62 (m, 2H), 6.54 (d, 1H), 6.18 (m, 1H), 7.39 (d, 1H), 4.94 (m, 4H), 4.15 (m, 2H), 3.76 (m, 2H), 3.44 (s, 3H), 3.10 (m, 2H), 1.28 (d, 3H).

The following compounds are prepared from compounds obtained as described

10 Examples 75-87 using the methods described above.

Example	Name	m/z [M+H]
618	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(4-chloro-thiophen-2-yloxy)-acetyl]-3(S)-methoxymethyl-6-methyl-piperazin-2-one	490, 492 Cl pattern
619	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-3-yloxy)-acetyl]-3(S)-methoxymethyl-6-methyl-piperazin-2-one	490, 492 Cl ₂ pattern
620	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-chloro-4-fluoro-phenoxy)-acetyl]-3(S)-methoxymethyl-6-methyl-piperazin-2-one	502, 504 Cl ₂ pattern
621	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3,5-dichloro-phenoxy)-acetyl]-3(S)-methoxymethyl-6-methyl-piperazin-2-one	502, 504 Cl pattern
622	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(2,5-dichloro-phenyl)-acryloyl]-3(S)-methoxymethyl-6-methyl-piperazin-2-one	514
623	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-2-methyl-phenoxy)-	498, 500

	acetyl]-3(S)-methoxymethyl-6-methyl-piperazin-2-one	Cl ₂ pattern
624	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(2,5-dichloro-phenoxy)-acetyl]-3(S)-methoxymethyl-6-methyl-piperazin-2-one	518
625	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(3-chloro-phenoxy)-acetyl]-3-(S)-methoxymethyl-6-methyl-piperazin-2-one	484
626	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-propionyl]-3(S)-ethyl-6-methyl-piperazin-2-one	472, 474 Cl pattern
627	1-(4-Amino-quinazolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3(S)-ethyl-6-methyl-piperazin-2-one	474
628	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3(S)-ethyl-6-methyl-piperazin-2-one	514, 516 Br pattern
629	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3(S)-ethyl-6-methyl-piperazin-2-one	470, 472 Cl pattern
630	(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-methoxymethyl-6-methyl-piperazin-2-one	486, 488 Cl pattern
631	(S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3-methoxymethyl-6-methyl-piperazin-2-one	530, 532 Br pattern
632	1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-carbonyl)-3(S)-6-dimethyl-piperazin-2-one	480 Cl pattern
633	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3(S)-6-dimethyl-piperazin-2-one	500, 502 Br pattern
634	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3(S)-6-dimethyl-piperazin-2-one	456, 458 Cl pattern
635	1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-6-methyl-piperazin-2-one	442, 444 Cl pattern

EXAMPLE 636. 4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide.

The title compound is prepared as described in EXAMPLE 436 using 1-(4-amino-

quinazoline-7-ylmethyl)-3-methoxymethyl-piperazine-2-one, EXAMPLE 75, and 4-chlorophenyl

5 isocyanate. ¹H NMR (DMSO-d₆, 300 MHz) δ 9.77 (bs, 2H), 8.81 (s, 1H), 8.70 (s, 1H), 8.40 (d, 1H), 7.64 (d, 1H), 7.61 (s, 1H), 7.49 (d, 2H), 7.28 (d, 2H), 4.88 (m, 1H), 4.80 (AB, 2H), 4.19 (m, 1H), 3.96 (m, 1H), 3.74-3.42 (m, 4H), 3.28 (s, 3H). ESI MS, [M+H]⁺=455,457 (Cl pattern). Anal. (C₂₂H₂₃CIN₆O₃TFA 1.5H₂O) C, H, N.

EXAMPLE 637. 4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methyl-3-oxo-piperazine-1-carboxylic acid (5-chloro-thiophen-2-yl)-amide.

The title compound is prepared as described in EXAMPLE 438 using 1-(4-amino-quinazoline-7-ylmethyl)-3-methyl-piperazine-2-one (EXAMPLE 80) and 5-chloro-thiophene-2-carbonyl azide (EXAMPLE 38). ^1H NMR (DMSO-d₆, 300 MHz) δ 10.01 (s, 1H), 9.73 (bs, 2H), 8.83 (s, 1H), 8.39 (d, 1H), 7.65 (d, 1H), 7.58 (s, 1H), 6.79 (d, 1H), 6.44 (d, 1H), 4.85 (d, 1H), 4.71 (m, 1H), 4.69 (d, 1H), 4.17 (d, 1H), 3.50 (m, 3H), 1.45 (d, 3H). ESI MS, $[\text{M}+\text{H}]^+=431,433$ (Cl pattern). Anal. $(\text{C}_{19}\text{H}_{19}\text{ClN}_6\text{O}_2\text{S}\cdot\text{TFA}\cdot1.9\text{H}_2\text{O})$ C, H, N.

10 EXAMPLE 638. 4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (5-chloro-thiophen-2-yl)-amide.

The title compound is prepared as described in EXAMPLE 439 using 1-(4-amino-quinazoline-7-ylmethyl)-3-methoxymethyl-piperazine-2-one (EXAMPLE 75) and 5-chloro-thiophene-2-carbonyl azide (EXAMPLE 38). ^1H NMR (DMSO-d₆, 300 MHz) δ 10.00 (s, 1H), 9.73 (bs, 2H), 8.82 (s, 1H), 8.40 (d, 1H), 7.65 (d, 1H), 7.60 (s, 1H), 6.80 (d, 1H), 6.42 (d, 1H), 4.86 (d, 1H), 4.80 (m, 1H), 4.70 (d, 1H), 4.18 (d, 1H), 3.96 (dd, 1H), 3.60 (m, 4H), 3.30 (s, 3H). ESI MS, $[\text{M}+\text{H}]^+=461,463$ (Cl pattern). Anal. $(\text{C}_{20}\text{H}_{21}\text{ClN}_6\text{O}_3\text{S}\cdot\text{TFA}\cdot1.1\text{H}_2\text{O})$ C, H, N.

The following compounds are prepared using the methods described above.

Example	Name	m/z $[\text{M}+\text{H}]$
639	4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-(2-methoxy-ethyl)-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide	469
640	4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-butyl-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide	467, 469 Cl pattern
641	4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (5-bromo-thiophen-2-yl)-amide	505, 507
642	4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (5-chloro-thiophen-3-yl)-amide	461, 463
643	4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (4-chloro-thiophen-2-yl)-amide	461
644	4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-(S)-2-propyl-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide	453, 455 Cl pattern
645	4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (3-bromo-phenyl)-amide	499

646	4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-(2S)-propyl-piperazine-1-carboxylic acid (4-chloro-thiophen-2-yl)-amide	459, 461
647	4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-(S)-2-propyl-piperazine-1-carboxylic acid (5-chloro-2-methoxy-phenyl)-amide	483, 485 Cl pattern
648	4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (4-bromo-2-chloro-phenyl)-amide	533, 535
649	4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (4-trifluoromethoxy-phenyl)-amide	505
650	4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (4-fluoro-phenyl)-amide	439
651	4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (2,4-dichloro-phenyl)-amide	489, 491
652	4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (2,4-difluoro-phenyl)-amide	457
653	4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (3-chloro-phenyl)-amide	455
654	4-(4-Amino-quinazolin-7-ylmethyl)-3-oxo-(2S)-propyl-piperazine-1-carboxylic acid (5-chloro-thiophen-2-yl)-amide	459, 460 Cl pattern
655	4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methyl-3-oxo-piperazine-1-carboxylic acid (6-chloro-pyridin-3-yl)-amide	426, 428
656	4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (4-bromo-phenyl)-amide	499, 501
657	4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methyl-3-oxo-piperazine-1-carboxylic acid (4-bromo-phenyl)-amide	486, 488
658	4-(4-Amino-quinazolin-7-ylmethyl)-2-(S)-methoxymethyl-5-(R,S)-methyl-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide	469, 471
659	4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-ethyl-3-oxo-piperazine-1-carboxylic acid (4-bromo-phenyl)-amide	483, 485
660	4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-methyl-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide	425, 427
661	4-(4-Amino-quinazolin-7-ylmethyl)-(2S)-ethyl-3-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide	439, 441
662	4-(4-Amino-quinazolin-7-ylmethyl)-(S)-2-methoxymethyl-3-oxo-piperazine-1-carboxylic acid (5-chloro-4-methoxy-thiophen-2-yl)-	491, 493 Cl pattern

	amide	
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EXAMPLE 663. (3S, 5RS)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-3,5-dimethyl-piperazin-2-one.

(3S,5RS)-1-(4-Amino-quinazolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one (260 mg, 0.56 mmol), EXAMPLE 88, is dissolved in 5 mL of DMF. Potassium carbonate (193.4 mg, 1.4 mmol) is added followed by the addition of 2-bromomethyl-6-chloro-benzo[b]thiophene (218 mg, 0.84 mmol), EXAMPLE 5. Reaction is left to stir overnight. The crude mixture is purified by reverse phase HPLC (10 -70% ACN/H₂O) to afford the product (27 mg, 6%) as a clear wax with a melting point of 130-131 °C . C₂₄H₂₄CIN₅OS MS m/z: 466, 468.

10 EXAMPLE 664. (3S, 5S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,5-dimethyl-piperazin-2-one, and

EXAMPLE 665. (3S,5R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,5-dimethyl-piperazin-2-one.

(3S,5RS)-1-(4-Amino-quinazolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one (60 mg, 0.13 mmol) is dissolved in 1 mL of DMF. Potassium carbonate (53 mg, 0.39 mmol) is added followed by the addition of 3-bromoallyl-5-chloro-thiophene (75 mg, 0.32 mmol). Reaction is left to stir overnight. The two epimers are separated by reverse phase HPLC (10 -70% ACN) in 43% yield.

The major epimer is assigned as (3S, 5S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,5 -dimethyl-piperazin-2-one trifluoroacetic acid salt (30.8 mg) and is isolated as a yellow solid with a melting point of 69-72 °C . C₂₂H₂₄CIN₅OS MS m/z: 442, 444.

The minor epimer is assigned as (3S, 5R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,5-dimethyl-piperazin-2-one trifluoroacetic acid salt (13.1 mg) with a melting point of 67-70 °C . C₂₂H₂₄CIN₅OS MS m/z: 442, 444. 1H NMR (CD₃OD) δ: 8.67 (s, 1H); 8.31 (d, 1H, J = 8.56 Hz); 7.83 (s, 1H); 7.74 (d, 2H, J = 8.56 Hz); 7.14 (d, 1H, J = 15.6 Hz); 6.92 (d, 1H, J = 3.74 Hz); 6.10-6.03 (m, 1H); 5.0-4.74 (m, 2H); 4.25-3.63 (m, 6 H); 1.78 (d, 3H, J = 7.03 Hz); 1.50 (d, 3H, J = 6.47 Hz).

30 EXAMPLE 666. (3S, 5R)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-3,5-dimethyl-piperazin-2-one.

(3S,5R)-1-(4-Amino-quinazolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one (43 mg, 0.123 mmol), minor epimer from EXAMPLE 88, Part D, is taken up in methylene chloride to this is added triethylamine (0.034 ml, 0.25 mmol) followed by 2-(5-chloro-thiophen-2-yl)-ethenesulfonyl chloride (40 mg, 0.16 mmol), EXAMPLE 3. The reaction is stirred overnight, and

the crude material is purified by preparative thin layer chromatography (15 % methanol/CH₂Cl₂). The product (1.4 mg, 2.3%) is isolated as a yellow wax. C₂₁H₂₂CIN₅O₃S₂ MS m/z: 492, 494. 1H NMR (CD₃OD) δ 8.36 (s, 1H); 8.03 (d, 1H, J = 7.5 Hz); 7.61 (s, 1H); 7.49-7.44 (m, 2H); 7.19 (d, 1H, J = 3.83 Hz); 6.98 (d, 1H, J = 3.75 Hz); 6.76 (d, 1H, J = 15.1 Hz); 4.86-4.71 (m, 2H); 4.45-4.39 (m, 1H); 4.13-4.09 (m, 1H); 3.64-3.7 (m, 2H); 1.63 (d, 3H, J = 7.09 Hz); 1.33 (d, 3H, J = 6.80 Hz).

EXAMPLE 667. (3S, 5S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-3,5-dimethyl-piperazin-2-one.

10 The product (7 mg, 9.4 %) is isolated as a yellow solid with a melting point of 218-221 °C. C₂₁H₂₂CIN₅O₃S₂ MS m/z: 492, 494. 1H NMR (CD₃OD) δ 8.37 (s, 1H); 8.10 (d, 1H, J = 8.57 Hz); 7.61-7.45 (m, 3H); 7.24 (d, 1H, J = 3.94 Hz); 6.98 (d, 1H, J = 3.85 Hz); 6.71 (d, 1H, J = 15.1 Hz); 4.76 (s, 2H); 4.32 (m, 1H); 3.71 (m, 1H); 3.36 (m, 2H); 1.62 (d, 3H, J = 7.06 Hz); 1.20 (d, 3H, J = 6.63 Hz).

15 **EXAMPLE 668. (3S, 5S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-sulfonyl)-3,5-dimethyl-piperazin-2-one.**

The desired product (5.4 mg, 8.5 %) is isolated as yellow solid with a melting point of 224-226 °C. C₂₃H₂₂CIN₅O₃S₂ MS m/z: 516, 518.

20 **EXAMPLE 669. (3S, 5S)-1-(4-Amino-quinazolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3,5-dimethyl-piperazin-2-one.**

To a solution of (3S,5S)-1-(4-amino-quinazolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one (42 mg, 0.147 mmol), major epimer from EXAMPLE 88, Part D, in 2 mL of DMF is added TBTU (52 mg, 0.162 mmol), triethylamine (0.02 mL, 0.162 mmol) and 3-(5-chloro-thiophen-2-yl)-acrylic acid (28 mg, 0.15 mmol), EXAMPLE 25. After stirring for two hours, the reaction mixture is directly purified by reverse phase HPLC (10-70 % ACN/H₂O). The product (35.5 mg, 36%) is isolated as a yellow solid with a melting point of 116-120 °C. C₂₂H₂₂CIN₅O₂S: MS m/z: 456, 458. Anal. calcd. for C₂₂H₂₂CIN₅O₂S•C₂HF₃O₂: C, 50.57; H, 4.07; N, 12.29. Found: C, 46.48; H, 3.64; N, 11.04.

EXAMPLE 670. (3S, 5R)-4-(4-Amino-quinazolin-7-ylmethyl)-2,6-dimethyl-oxo-piperazine-1-carboxylic acid (4-bromo-phenyl)-amide.

4-Bromo-phenyl isocyanate (20.8 mg, 0.105 mmol) is added to solution of (3S,5R)-1-(4-amino-quinazolin-7-ylmethyl)-3,5-dimethyl-piperazin-2-one (30 mg, 0.105 mmol), minor epimer

from EXAMPLE 88, Part D, in 1 mL of DMF. The reaction is stirred for two hours at room temperature. The product (21.4 mg, 33%) is isolated from reverse phase HPLC (10 -70% ACN/H₂O) as white solid. The melting of the compound is 142-144 °C. C₂₂H₂₃BrN₆O₂ MS m/z: 483, 485. Anal. cald. for C₂₂H₂₃BrN₆O₂•2C₂HF₃O₂: C, 43.90; H, 3.54; N, 11.81. Found: C, 44.52; H, 3.86; N, 12.44.

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EXAMPLE 671. (3S, 5S)-4-(4-Amino-quinazolin-7-ylmethyl)-2,6-dimethyl-oxo-piperazine-1-carboxylic acid (4-bromo-phenyl)-amide.

10 The desired product (35 mg, 47%) is isolated as a white solid with a melting point of 142-144°C. C₂₂H₂₃BrN₆O₂ MS m/z: 483, 485. Anal. cald. for C₂₂H₂₃BrN₆O₂•2C₂HF₃O₂: C, 43.90; H, 3.54; N, 11.81. Found: C, 44.73; H, 3.59; N, 12.38.

15 EXAMPLE 672. (3S, 5S)-4-(4-Amino-quinazolin-7-ylmethyl)-2,6-dimethyl-oxo-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide.

20 The product (24.7 mg, 50%) is obtained as a white solid with a melting point of 123-125 °C. C₂₂H₂₃ClN₆O₂ MS m/z: 439, 441. Anal. cald. for C₂₂H₂₃ClN₆O₂•2C₂HF₃O₂: C, 46.82; H, 3.78; N, 12.60. Found: C, 47.69; H, 4.33; N, 13.32.

25 EXAMPLE 673. 1-(4-Aminoquinolin-7-ylmethyl)-4-(6-chlorobenzo[b]thiophen-2-sulfonyl)-piperazin-2-one.

30 A. 1-(4-Chloroquinolin-7-ylmethyl)-4-(6-chlorobenzo[b]thiophen-2-sulfonyl)-piperazin-2-one.
1-(4-chloroquinolin-7-ylmethyl)-3-(S)-methylpiperazin-2-one hydrochloride (0.49 g, 1.4 mmol), EXAMPLE 89, is treated with acetonitrile (20 mL), triethyl amine (1.2 ml, 8.4 mmol) and a solution of 6-chlorobenzo[b]thiophen-2-sulfonyl chloride (0.41 g, 1.54 mmol), EXAMPLE 1, in acetonitrile (10 mL) at 0°C. After 2 h the solution is poured into water and extracted with ethyl acetate. The organic layer is washed with water, dried over sodium sulfate and concentrated to yield the title compound (0.45 g, 0.95 mmol). MS m/z: 506, [M+1]⁺; ¹H NMR (CD₃OD, 300 MHz) δ 8.8 (d, 1H), 8.15 (d, 1H), 7.9 (d, 2H), 7.85 (s, 1H), 7.4-7.5 (m, 2H), 6.8 (s, 1H), 4.8 (s, 2H), 4.0 (s, 2H), 3.4-3.45 (m, 4H).

35 B. 1-(4-Azidoquinolin-7-ylmethyl)-4-(6-chlorobenzo[b]thiophen-2-sulfonyl)-piperazin-2-one
1-(4-Chloroquinolin-7-ylmethyl)-4-(6-chlorobenzo[b]thiophen-2-sulfonyl)-piperazin-2-one (0.52 g, 1.03 mmol) is dissolved in DMF (15 mL), treated with sodium azide (0.52 g, 8.0 mmol), tetrabutyl ammonium chloride (0.1 g, 0.36 mmol) and heated to 65 °C overnight. The reaction

mixture is cooled, poured into water and extracted with ethyl acetate. The organic layer is washed with water, dried (sodium sulfate) and concentrated to give the title compound (0.5 g, 1.04 mmol). ¹H NMR (CD₃OD, 300 MHz) δ 9.0 (d, 1H), 8.2 (d, 1H), 8.0 (s, 1H), 7.9 (d, 2H), 7.8 (d, 1H), 7.6 (d, 1H), 7.5 (d, 1H), 6.9 (s, 1H), 4.85 (s, 2H), 4.0 (s, 2H), 3.5-3.7 (m, 4H).

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C. 1-(4-Aminoquinolin-7-ylmethyl)-4-(6-chlorobenzo[b]thiophen-2-sulfonyl)-piperazin-2-one

A suspension of 1-(4-azidoquinolin-7-ylmethyl)-4-(6-chlorobenzo[b]thiophen-2-sulfonyl)-piperazin-2-one (0.50 g, 1.04 mmol) in 100 mL of acetic acid/methanol (~ 1:10) is treated with 10% Pd/C (0.15 g) and stirred under hydrogen for 1.5 hours. The resulting solution is filtered through Celite and the filtrate is evaporated in vacuo. The organic layer is concentrated and the residue is purified by reverse phase HPLC (gradient elution of 30 % of 0.1 % aqueous TFA/acetonitrile to 100 % acetonitrile) and lyophilized to give the title compound (0.39 g, 0.86 mmol). MS (ISP) m/z 487, 489, (M+H), Cl pattern.

15 The following compounds are prepared from the compound of Example 89 or 91 using the methods described above.

Example	Name	m/z [M+H]
674	1-(4-Amino-quinolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethene-sulfonyl]-piperazin-2-one	463, 465
675	(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-3-methyl-piperazin-2-one	501, 503
676	(3S,5S)-1-(4-Amino-quinolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-3,5-dimethyl-piperazin-2-one	491, 493
677	(3S,5R)-1-(4-Amino-quinolin-7-ylmethyl)-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-3,5-dimethyl-piperazin-2-one	491, 493
678	(S,R)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid	531, 533
679	1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid methylamide	544
680	1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid ethylamide	558
681	1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-oxo-piperazine-2-carboxylic acid dimethylamide	558

682	1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-6-(morpholine-4-carbonyl)-piperazin-2-one	600
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EXAMPLE 683. (S)-1-(4-Aminoquinolin-7-ylmethyl)-4-[3-(5-chlorothiophen-2-yl)-allyl]-3-methylpiperazin-2-one.

A. (S)-1-(4-Chloroquinolin-7-ylmethyl)-4-[3-(5-chlorothiophen-2-yl)-allyl]-3-methylpiperazin-2-one.

(S)-1-(4-chloroquinolin-7-ylmethyl)-3-methylpiperazin-2-one hydrochloride (0.25 g, 1.0 mmol), EXAMPLE 91, is treated with 2-(3-Bromo-(E)-propenyl)-5-chloro-thiophène (0.35 g 1.2 mmol), EXAMPLE 17, and potassium carbonate (0.5 g, 3 mmol). The resulting suspension is sonicated for 10 minutes then stirred vigorously for 16 h at ambient temperature. The reaction mixture is poured into water and extracted with ethyl acetate (2 X 150 mL). The organic layer is washed with water (4 X 200 mL), dried over sodium sulfate and concentrated. The residue is chromatographed (3 % methanol/methylene chloride) to give the title compound (0.31 g, 0.73 mmol).

B. (S)-1-(4-Aminoquinolin-7-ylmethyl)-4-[3-(5-chlorothiophen-2-yl)-allyl]-3-methylpiperazin-2-one.

(S)-1-(4-Chloroquinolin-7-ylmethyl)-4-[3-(5-chlorothiophen-2-yl)-allyl]-3-methylpiperazin-2-one (0.35 g, 0.82 mmol) is treated with phenol (2 g) and ammonium acetate (0.7 g, 9.1 mmol) and heated to 120 °C in a sealed vessel for 1 hour. Upon cooling, the solution is partitioned between 2 N NaOH and ethyl acetate. The organic layer is separated and washed with fresh 2 N NaOH (3 X 100 mL) and water. The organic layer is concentrated and the residue is purified by reverse phase HPLC to give the title compound as a white solid (0.15 g, 0.35 mmol). MS (ISP) m/z 427, 429, (M+H), Cl pattern.

25 The following compounds are prepared from starting materials prepared as described in Examples 61-64, 89 or 91 using the methods described above.

Example	Name	m/z [M+H]
684	1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-piperazin-2-one	413, 415
685	(3S, 5R)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-benzo[b]thiophen-2-ylmethyl)-3,5-dimethyl-piperazin-2-one	465, 467
686	(3S, 5S)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-	464

	benzo[b]thiophen-2-ylmethyl)-3,5-dimethyl-piperazin-2-one	
687	(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)-3-methyl-piperazin-2-one	446, 448
688	(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-naphthalen-2-ylmethyl)-3-methyl-piperazin-2-one	444
689	(3S,5S)-1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,5-dimethyl-piperazin-2-one	441, 443
690	(3S,5R)-1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]-3,5-dimethyl-piperazin-2-one	441, 443
691	1-(4-Amino-quinolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)-piperazin-2-one	420, 422
692	(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-(6-chloro-naphthalen-2-ylmethyl)-3-ethyl-piperazin-2-one	458
693	1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-allyl]- (S)-3-((R)-1-methoxy-ethyl)-piperazin-2-one	470
694	1-(4-Amino-quinolin-7-ylmethyl)-4-(7-chloro-isoquinolin-3-ylmethyl)- (S)-3-((R)-1-methoxy-ethyl)-piperazin-2-one	489
695	(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)- 3-methoxymethyl-piperazin-2-one	464, 466
696	(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-(5-chloro-1H-indol-2-ylmethyl)- 3-methyl-piperazin-2-one	434, 436
697	4-(5-Chloro-1H-indol-2-ylmethyl)-1-[4-(2-hydroxy-ethylamino)- quinolin-7-ylmethyl]-piperazin-2-one	464
698	(S)-4-(5-Chloro-1H-indol-2-ylmethyl)-1-(4-ethylamino-quinolin-7- ylmethyl)-3-methyl-piperazin-2-one	462
699	(S)-4-(5-Chloro-1H-indol-2-ylmethyl)-1-(4-ethylamino-quinolin-7- ylmethyl)-3-methoxymethyl-piperazin-2-one	492
700	(S)-4-(5-Chloro-1H-indol-2-ylmethyl)-3-methyl-1-(4-methylamino- quinolin-7-ylmethyl)-piperazin-2-one	448
701	(S)-4-(5-Chloro-1H-indol-2-ylmethyl)-3-methoxymethyl-1-(4- methylamino-quinolin-7-ylmethyl)-piperazin-2-one	478
702	(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)- allyl]-3-methyl-4-oxy-piperazin-2-one	443

EXAMPLE 703. (S)-1-(4-Aminoquinolin-7-ylmethyl)-4-[3-(4-bromothiophen-2-yl)acryloyl]-3-methyl-piperazin-2-one.

A. (S)-1-(4-Chloroquinolin-7-ylmethyl)-4-[3-(4-bromothiophen-2-yl)acryloyl]-3-methyl piperazin-2-one.

(S)-1-(4-chloroquinolin-7-ylmethyl)-3-methylpiperazin-2-one hydrochloride (0.35 g, 1.4 mmol), EXAMPLE 91, is treated with DMF (20 mL), 3-(4-bromothiophen-2-yl)-(E)-acrylic acid (0.32 g, 1.4 mmol), prepared according to EXAMPLE 26, using 4-bromothiophene-2-carboxaldehyde, triethyl amine (0.21 ml, 1.4 mmol) and 2-(1H-benzotriazol-1-yl)1,1,3,3-tertamethyluronium tetrafluoroborate (0.45 g, 1.4 mmol) and heated to 50 °C for 5 minutes. The reaction mixture is stirred at ambient temperature for 16 h then partitioned between ethyl acetate and water. The organic layer is concentrated and the residue is chromatographed (5% methanol/methylene chloride) to give crude title compound (0.5 g, 0.9 mmol). MS m/z: [M+H]⁺ = 504. ¹H NMR (CDCl₃, 300 MHz) δ 8.9 (d, 1H), 8.2-8.3(m, 2H), 8.0 (s, 1H), 7.7-7.8 (m, 1H), 7.4 (s, 1H), 7.3-7.4 (m, 1H), 6.7-6.8 (m, 1H), 6.6 (d, 1H), 5.1-5.2 (m, 1H), 4.6-4.7 (m, 2H), 3.4-3.6 (m, 2H), 3.0-3.3 (m, 2H), 1.5 (d, 3H).

B. (S)-1-(4-Aminoquinolin-7-ylmethyl)-4-[3-(4-bromothiophen-2-yl)acryloyl]-3-methyl-piperazin-2-one.

(S)-1-(4-Chloroquinolin-7-ylmethyl)-4-[3-(4-bromothiophen-2-yl)acryloyl]-3-methyl piperazin-2-one (0.50 g, 0.9 mmol) is treated with phenol (~ 2 g) and ammonium acetate (0.5 g, 6.4 mmol) and heated to 120 °C in a sealed vessel for 1 hour. Upon cooling, the solution is partitioned between 2 N NaOH and ethyl acetate. The organic layer is separated and washed with fresh 2 N NaOH (3 X 100 mL) and water. The organic layer is concentrated and the residue is purified by reverse phase HPLC (gradient elution of 10 % of 0.1 % aqueous TFA/acetonitrile to 100 % acetonitrile) to give the title compound (0.22 g, 0.56 mmol). MS m/z: [M+H]⁺ = 485, 487, Cl pattern. ¹H NMR (CD₃OD, 300 MHz) δ 8.2-8.4 (m, 2H), 7.7-7.8 (m, 2H), 7.6 (d, 1H), 7.5 (s, 1H), 7.3 (s, 1H), 6.9-7.0 (m, 1H), 6.7 (d, 1H), 5.0-5.1 (m, 1H), 4.9 (q, 2H), 4.3-4.4 (m, 1H), 3.5-3.7 (m, 2H), 3.3-3.4 (m, 2H), 1.5 (d, 3H).

The following compounds are prepared from starting materials prepared as described in Examples 75-87 using the methods described above.

Example	Name	m/z [M+H]
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704	1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3(S)-ethyl-6-methyl-piperazin-2-one	469 CI pattern
705	4-[3-(5-Chloro-thiophen-2-yl)-acryloyl]-3(S)-3-ethyl-1-(4-hydroxyamino-quinolin-7-ylmethyl)-piperazin-2-one	471, 473
706	1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-piperazin-2-one	427, 429
707	(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-ethyl-piperazin-2-one	454
708	(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-methyl-piperazin-2-one	441, 443
709	1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-piperazin-2-one	471, 473
710	(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-methoxymethyl-piperazin-2-one	470
711	(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(4-bromo-thiophen-2-yl)-acryloyl]-3-ethyl-piperazin-2-one	498
712	(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-ethyl-piperazin-2-one	458
713	(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-[(5-chloro-thiophen-2-yloxy)-acetyl]-3-methoxymethyl-6-methyl-piperazin-2-one	488
714	1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-(1-(R)-methoxy-ethyl)-piperazin-2-one	484
715	1-(4-Aminoquinolin-7-ylmethyl)-4-[3-(4-bromothiophen-2-yl)-acryloyl]-3-(S)-(1-(R)-methoxyethyl)-piperazin-2-one trifluoroacetate	528
716	1-(4-Aminoquinolin-7-ylmethyl)-4-[(5-chlorothiophen-2-yloxy-acetyl)-3-(S)-(1-(R)-methoxyethyl)-piperazin-2-one trifluoroacetate	488
717	(S)-1-(4-Amino-quinolin-7-ylmethyl)-4-[3-(5-chloro-thiophen-2-yl)-acryloyl]-3-ethyl-piperazin-2-one	454

EXAMPLE 718. 1-(4-Aminocinnolin-7-ylmethyl)-4-[2-(5-chlorothiophen-2-yl)-ethenesulfonyl]-piperazin-2-one.

A. 1-(4-Chlorocinnolin-7-ylmethyl)-4-[2-(5-chlorothiophen-2-yl)-ethenesulfonyl]-piperazin-2-one

5 1-(4-chlorocinnolin-7-ylmethyl)-piperazin-2-one hydrochloride (0.14 g, 0.4 mmol),

EXAMPLE 90, is treated with acetonitrile (20 mL), triethylamine (2 mL, 14 mmol) and 2-(5-chlorothiophen-2-yl)ethene-sulfonyl chloride (0.097 g, 0.4 mmol), EXAMPLE 3, at 0°C. The

solution is warmed to ambient temperature over 1.5 h and diluted with ethyl acetate. The solution is washed with 10 % sodium bicarbonate solution and water, dried (sodium sulfate) and concentrated to yield the title compound (0.17 g, 0.35 mmol). MS m/z: [M+H]⁺ = 483; ¹H NMR (CDCl₃, 300 MHz) δ 9.4 (s, 1H), 8.4 (s, 1H), 8.3 (d, 1H) 7.85 (d, 1H), 7.7 (d, 1H), 7.1 (d, 1H), 6.95 (d, 1H), 6.35 (d, 1H), 4.9 (s, 2H), 4.0 (s, 2H), 3.4-3.5 (m, 4H).

B. 1-(4-Aminocinnolin-7-ylmethyl)-4-[2-(5-chlorothiophen-2-yl)-ethenesulfonyl]-piperazin-2-one

1-(4-Chlorocinnolin-7-ylmethyl)-4-[2-(5-chlorothiophen-2-yl)-ethenesulfonyl]-piperazin-2-one (0.06 g, 0.12 mmol) is treated with phenol (0.20 g) and ammonium acetate (0.2 g, 2.6 mmol) and heated to 120 °C for 45 minutes. The reaction mixture is cooled, diluted with ethyl acetate and washed with 1 N NaOH (3 X 100 mL) and water. The organic layer is concentrated and the residue is purified by reverse phase HPLC (20 % aqueous TFA (0.1 %)/acetonitrile to 100 % acetonitrile). Fractions containing the desired product are lyophilized to obtain the title compound (0.02 g, 0.043 mmol). MS m/z: [M+H]⁺ = 464; ¹H NMR (CD₃OD, 300 MHz) δ 8.6 (s, 1H), 8.4 (d, 1H), 7.75 (d, 1H), 7.65 (d, 1H), 7.35 (d, 1H), 7.1 (d, 1H), 6.8 (d, 1H), 4.9 (s, 2H), 4.05 (s, 2H), 3.6 (m, 4H).

EXAMPLE 719. 4-(6-Chloro-thieno[2,3-b]pyridine-2-sulfonyl)-1-[2-(pyridin-4-ylamino)-ethyl]-piperazin-2-one.

1-[2-(Pyridin-4-ylamino)-ethyl]-piperazin-2-one (0.20 mmol), EXAMPLE 90, is dissolved in MeCN (5 mL) and treated with 4-methylmorphorline (0.055 ml, 0.50 mmol). 6-Chloro-thieno[2,3-b]pyridine-2-sulfonyl chloride (54 mg, 0.20 mmol) in MeCN (2 mL) is added dropwise. The reaction mixture is stirred at r.t. for 1.5 h, then subjected to HPLC purification, to give the title compound as white solid (0.021 g, 0.037 mmol). MS m/z 452, 454 (M+1); ¹H NMR (CD₃OD, 300 MHz) δ 8.37 (d, 1H), 8.30 (b, 1H), 8.12 (d, 1H), 8.02 (s, 1H), 7.97 (d, 1H), 7.57 (d, 1H), 6.98 (d, 1H), 6.88 (d, 2H), 3.73 (s, 2H), 3.60-3.48 (m, 8H).

EXAMPLE 720. 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[2-(methyl-pyridin-4-yl-amino)-ethyl]-piperazin-2-one.

A portion (~50%) of the crude 1-[2-((Methyl)-(pyridin-4-yl)-amino)-ethyl]-piperazin-2-one, EXAMPLE 93 is reacted with 6-chloro-benzo[b]thiophene-2-sulfonyl chloride (54 mg, 0.20 mmol), EXAMPLE 1, using same procedure as described in EXAMPLE 719. The residue obtained after HPLC purification is subjected to silica gel chromatography using NH₄OH/MeOH/CH₂Cl₂ (1:4:95) as eluant to give title compound (30 mg, 0.064 mmol) as a white solid. MS m/z 465, 457 (M+1); ¹H NMR (CDCl₃, 300 MHz) δ 8.15 (d, 2H), 7.88 (s, 1H), 7.85 (d,

1H), 7.79 (s, 1H), 7.47 (d, 1H), 6.47 (d, 2H), 3.80 (s, 2H), 3.50 (m, 4H), 3.43 (d, 2H), 3.30 (d, 2H), 2.98 (s, 3H).

EXAMPLE 721. 4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-1-[2-(3-methyl-pyridin-4-

ylamino)-ethyl]-piperazin-2-one.

1-[2-(3-Methylpyridin-4-yl-amino)-ethyl]-piperazin-2-one (38 mg, 0.16 mmol), EXAMPLE 94, is reacted with 2-(5-chloro-thiophen-2-yl)-ethenesulfonyl chloride (40 mg, 0.16 mmol), EXAMPLE 3, using the same procedure as described in EXAMPLE 719. Reverse phase HPLC purification gives the title compound (29 mg, 0.052 mmol) as a white solid. MS m/z 441, 443 (M+H); ¹H NMR (CD₃OD, 300 MHz) δ 8.08 (d, 1H), 7.98 (s, 1H), 7.56 (d, 1H), 7.30 (d, 1H), 7.02 (s, 1H), 7.00 (d, 1H), 6.78 (d, 1H), 3.87 (s, 2H), 3.70-3.50 (m, 8H), 2.15 (s, 3H).

The following compounds are prepared from starting materials obtained as described in Examples 92-97 using the methods described above.

15

Example	Name	m/z [M+H]
722	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[2-(pyridin-4-ylamino)-ethyl]-piperazin-2-one	520 (M+)
723	1-[2-(Pyridin-4-ylamino)-ethyl]-4-(thieno[2,3-b]pyridine-2-sulfonyl)-piperazin-2-one	417
724	4-(5'-Chloro-[2,2']bithiophenyl-5-sulfonyl)-1-[2-(pyridin-4-ylamino)-ethyl]-piperazin-2-one	483, 485
725	1-[2-(Pyridin-4-ylamino)-ethyl]-4-(thieno[3,2-b]pyridine-2-sulfonyl)-piperazin-2-one	418
726	4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-1-[2-(pyridin-4-ylamino)-ethyl]-piperazin-2-one	427, 429
727	4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-1-[2-(methylpyridin-4-ylamino)-ethyl]-piperazin-2-one	441
728	4-(2-Benzo[b]thiophen-2-yl-ethenesulfonyl)-1-[2-(pyridin-4-ylamino)-ethyl]-piperazin-2-one	443
729	4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[2-(3-methyl-pyridin-4-ylamino)-ethyl]-piperazin-2-one	465, 467
730	4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-1-(2-pyrrolo[3,2-c]pyridin-1-yl-ethyl)-piperazin-2-one	450, 452

731	1-[2-(2-Amino-3-chloro-pyridin-4-ylamino)-ethyl]-4-[2-(5-chlorothiophen-2-yl)-ethenesulfonyl]-piperazin-2-one	476, 478
732	1-[2-(2-Amino-5-chloro-pyridin-4-ylamino)-ethyl]-4-[2-(5-chlorothiophen-2-yl)-ethenesulfonyl]-piperazin-2-one	476, 478
733	4-[2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl]-1-[2-(2,3,5,6-tetrachloro-pyridin-4-ylamino)-ethyl]-piperazin-2-one	563, 565, 567, 569
734	1-[2-(2-Amino-3,5,6-trichloro-pyridin-4-ylamino)-ethyl]-4-[2-(5-chlorothiophen-2-yl)-ethenesulfonyl]-piperazin-2-one	544, 546, 548
735	4-[3-(5-Chloro-thiophen-2-yl)-acryloyl]-1-[2-(pyridin-4-ylamino)-ethyl]-piperazin-2-one	391, 393

EXAMPLE 736. 4-(6-Chloro-benzo[b]thiophene-2-sulfonyl)-1-[2-(pyridazin-4-yl-amino)-ethyl]-piperazin-2-one.

1-[2-(Pyridazin-4-ylamino)-ethyl]-piperazin-2-one hydrochloride (0.5 g, 1.7 mmol),

EXAMPLE 95, is reacted with 6-chloro-benzo[b]thiophene-2-sulfonyl chloride (0.40 g, 1.5

5 mmol), EXAMPLE 1, using essentially the same procedure as described in EXAMPLE 719.

Reverse phase HPLC purification gives the title compound (0.34 g, 0.75 mmol) as a white solid.

MS m/z (M+H= 452); ¹H NMR (CD₃OD, 300 MHz) δ 8.6 (d, 1H), 8.4 (d, 1H), 8.05 (s, 1H), 8.05 (s, 1H), 7.9 (d, 1H), 7.5 (d, 1H), 7.2 (d, 1H), 3.8 (s, 2H), 3.4-3.7 (m, 8H).

10 EXAMPLE 737. 1-[3-(4-Amino-pyridin-3-yl)-propenyl]-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-piperazin-2-one.

4-[3-(4-tert-Butoxycarbonylamino-pyridin-3-yl)-propenyl]-3-oxo-piperazine-1-carboxylic acid tert-butyl ester from EXAMPLE 96, Part B (45 mg, 0.10 mmol) is dissolved in 20% TFA/CH₂Cl₂ and stirred at r.t. for 2 hours. The solution is concentrated to residue. The residue is dissolved in MeCN (2.5 ml) and treated with 4-methylmorphorline (0.027 ml, 0.25 mmol), 2-(5-Chloro-thiophen-2-yl)-ethenesulfonyl chloride (24 mg, 0.10 mmol), EXAMPLE 3, in MeCN (1 mL) is then added dropwise. The reaction mixture is stirred at r.t. for 1 h, then subjected to reverse phase HPLC purification, to give the title compound as white solid (0.040 g, 0.037 mmol). MS m/z 439, 441 (M+H); ¹H NMR (CD₃OD, 300 MHz) δ 8.20 (br, 1H), 8.10 (s, 1H), 8.08 (d, 1H), 7.60 (d, 1H), 7.53 (d, 1H), 7.35 (d, 1H), 7.21 (d, 1H), 7.07 (d, 1H), 6.82 (d, 1H), 5.27 (m, 1H), 3.88 (s, 2H), 3.60-3.50 (m, 4H), 3.30 (d, 2H).

The following compounds are prepared from starting materials obtained as described in Examples 92-97 using the methods described above.

Example	Name	m/z [M+H]
738	1-[3-(4-Amino-pyridin-3-yl)-propenyl]-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one	463, 465
739	1-[3-(4-Amino-pyridin-3-yl)-allyl]-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one	463, 465
740	1-[3-(4-Amino-pyridin-3-yl)-allyl]-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-piperazin-2-one	439, 441
741	1-[3-(4-Amino-pyridin-3-yl)-propyl]-4-(6-chloro-benzo[b]thiophene-2-sulfonyl)-piperazin-2-one	465, 467
742	1-[3-(4-Amino-pyridin-3-yl)-propyl]-4-[2-(5-chloro-thiophen-2-yl)-ethenesulfonyl]-piperazin-2-one	441, 443

5 EXAMPLE 743. 4-[2-(5-Chlorothiophen-2-yl)-ethenesulfonyl]-1-(2-pyrrolo[3,2-c]pyridin-1-ylethyl)-piperazin-2-one.

4-(Benzylxycarbonyl)-1-(2-pyrrolo[3,2-c]pyridin-1-ylethyl)-piperazin-2-one (0.028 g, 0.074 mmol), EXAMPLE 98, is treated with 4 % HCO₂H/MeOH (5 mL) and a catalytic amount of Pd black for 5 minutes. The reaction mixture is filtered washed with methanol and the filtrate is concentrated to a residue. The residue is treated with acetonitrile (3 mL) excess N-methylmorpholine (0.04 mL) and 2-(5-chlorothiophen-2-yl)ethene-sulfonyl chloride (0.018 g, 0.074 mmol), EXAMPLE 3, and processed as usual (EXAMPLE 719). Further chromatographic purification (NH₄OH/MeOH/CH₂Cl₂;1/4/95) yields the title compound: MS m/z 451, 453 (M+H); ¹H NMR (CDCl₃, 300 MHz) δ 8.93 (bs, 1H), 8.24 (bs, 1H), 7.41 (d, 1H), 7.23 (d, 1H), 7.14 (m, 2H), 6.94 (d, 1H), 6.68 (d, 1H), 6.18 (d, 1H), 4.43 (t, 2H), 3.67 (t, 2H), 2.88 (t, 2H), 2.66 (t, 2H).

EXAMPLE 744. 4-Prop-2-ynyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.

20 A. 2-(2-Oxo-4-prop-2-ynyl-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester.

A solution containing 2-(2-oxo-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (4.3 g, 13.0 mmol), EXAMPLE 69, in CH₃CN (250 mL) is cooled to 0°C. Potassium carbonate (1.98 g, 14.3 mmol) is added to the reaction mixture followed by propargyl bromide (1.55g, 13.0 mmol). The mixture is slowly warmed to ambient temperature and

maintained until complete consumption of starting material is observed by TLC (approx. 8 h). The mixture is concentrated to dryness and then partitioned between aqueous NaHCO₃ (200 mL) and CH₂Cl₂ (200 mL) and the layers are separated. The aqueous phase is extracted twice with CH₂Cl₂ (100 mL) and the combined organic phase is washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The crude residue is purified by flash silica gel chromatography (CH₂Cl₂ to 5% MeOH/CH₂Cl₂) to provide 3.38 g (70%) of the title compound as a pale yellow solid. ¹H NMR (300 MHz, CDCl₃) δ 1.69 (s, 9H), 2.34 (t, J = 2.4 Hz, 1H), 2.89 (m, 2H), 3.42 (s, 2H), 3.45 (d, J = 2.4 Hz, 2H), 3.52 (m, 2H), 4.95 (d, J = 1.4 Hz, 2H), 6.42 (br s, 1H), 7.88 (dd, J = 5.8, 0.8 Hz, 1H), 8.41 (d, J = 5.8 Hz, 1H), 8.78 (d, J = 0.8 Hz, 1H) ppm; MS (EI): m/z 368 (M⁺).

B. 4-Prop-2-ynyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.

To a solution containing 2-(2-oxo-4-prop-2-ynyl-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (1.3 g, 3.53 mmol) in CH₂Cl₂ (100 mL) is added TFA (20 mL) at 0 °C. After 6 h, the reaction mixture is concentrated to dryness and then partitioned between aqueous NaHCO₃ (500 mL) and CH₂Cl₂ (200 mL) and the layers are separated. The aqueous phase is extracted four times with CH₂Cl₂ (100 mL) and the combined organic phase is washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The crude residue is purified by flash silica gel chromatography (CH₂Cl₂ to 10% MeOH/CH₂Cl₂) to provide 616 mg (65%) of the title compound as a pale yellow solid.

¹H NMR (300 MHz, CDCl₃) δ 2.27 (app t, J = 2.4 Hz, 1H), 2.76 (m, 2H), 3.33 (s, 2H), 3.83 (d, J = 2.4 Hz, 2H), 3.45 (m, 2H), 4.57 (s, 2H), 6.47 (s, 1H), 7.23 (d, J = 5.7 Hz, 1H), 8.28 (d, J = 5.7 Hz, 1H), 8.85 (d, J = 0.9 Hz, 1H), 9.34 (br s, 1H) ppm; MS (EI): m/z 268 (M⁺).

EXAMPLE 745. 1,4-Bis-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.

A. 2-{4-[3-(4-tert-Butoxycarbonylamo-pyridin-3-yl)-prop-2-ynyl]-2-oxo-piperazin-1-ylmethyl}-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester.

A solution containing 2-(2-oxo-4-prop-2-ynyl-piperazin-1-ylmethyl)-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (100 mg, 0.27 mmol), EXAMPLE 743, (3-iodo-pyridin-4-yl)-carbamic acid tert-butyl ester (87 mg, 0.27 mmol), EXAMPLE 69, Part B, Et₃N (110 mg, 1.08 mmol), (Ph₃P)₄PdCl₂ (10 mg, 0.013 mmol), and CuI (1 mg, 0.008 mmol) in anhydrous DMF (5 mL) is stirred at ambient temperature. After 5 h, the reaction mixture is diluted with EtOAc (50 mL) and water (50 mL) and the layers are separated. The aqueous layer is extracted twice with EtOAc (25 mL) and the combined organic phase is washed with brine,

dried over anhydrous Na_2SO_4 , filtered and concentrated. The crude residue is purified by flash silica gel chromatography (CH_2Cl_2 to 10% MeOH CH_2Cl_2) to provide 77 mg (51%) of the title compound as a colorless oil. ^1H NMR (300 MHz, CDCl_3 , ~2:1 mixture of rotamers) major rotamer: δ 1.53 (s, 9H), 1.69 (s, 9H), 2.98 (m, 2H), 3.49 (s, 2H), 3.56 (m, 2H), 3.78 (s, 2H), 4.98 (s, 2H), 6.43 (s, 1H), 7.89 (m, 1H), 8.09 (m, 2H), 8.34 (m, 1H), 8.41 (m, 1H), 8.75 (m, 1H) ppm; 5 MS (ISP loop): m/z 561 (M+H).

B. 2-[4-(1-tert-Butoxycarbonyl-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-2-oxo-piperazin-1-ylmethyl]-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester.

10 1,8-Diazabicyclo[5.4.0]undec-7-ene (42 mg, 0.27 mmol) is added to a suspension containing 2-[4-[3-(4-tert-butoxycarbonylamino-pyridin-3-yl)-prop-2-ynyl]-2-oxo-piperazin-1-ylmethyl]-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (77 mg, 0.14 mmol) in anhydrous CH_3CN (10 mL) and the mixture is warmed to 50 °C. After 4 h, the reaction mixture is concentrated to dryness and the residue is partitioned between CH_2Cl_2 (50 mL) and water (50 mL) and the layers are separated. The aqueous layer is extracted twice with CH_2Cl_2 (25 mL) and the combined organic phase is washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated to provide 85 mg of the title compound as a crude solid which is used directly without further purification. ^1H NMR (300 MHz, CDCl_3) δ 1.68 (s, 9H), 1.70 (s, 9H), 2.91 (m, 2H), 3.41 (s, 2H), 3.49 (m, 2H), 4.26 (s, 2H), 4.95 (d, J = 1.1 Hz, 2H), 6.39 (d, J = 0.7 Hz, 1H), 6.68 (d, J = 0.7 Hz, 1H), 7.86 (m, 1H), 8.41 (m, 1H), 8.76 (br s, 1H), 8.82 (br s, 1H) ppm; 15 MS (EI): m/z 561 (M+H).

20 MS (EI): m/z 561 (M+H).

C. 1,4-Bis-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-piperazin-2-one.

25 To a solution containing 2-[4-(1-tert-Butoxycarbonyl-1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)-2-oxo-piperazin-1-ylmethyl]-pyrrolo[3,2-c]pyridine-1-carboxylic acid tert-butyl ester (85 mg, 0.14 mmol) in CH_2Cl_2 (5 mL) is added TFA (1 mL) at 0°C and the solution is allowed to slowly warm to ambient temperature. After 16 h, the reaction mixture is concentrated to dryness, diluted with water and purified by reverse-phase HPLC [Buffer A: water w/ 0.1% TFA; Buffer B: CH_3CN w/ 0.1% TFA; Gradient: 0% B to 45% B over 30 min] to provide 35 mg (36%, 30 two steps) of the title compound as a pale yellow, lyophilized solid.

35 ^1H NMR (300 MHz, $d_6\text{-DMSO}$) δ 2.80 (m, 2H), 3.25 (s, 2H), 3.37 (m, 2H), 3.93 (s, 2H), 4.76 (s, 2H), 6.88 (s, 1H), 6.94 (s, 1H), 7.85 (d, J = 6.6 Hz, 1H), 7.89 (d, J = 6.6 Hz, 1H), 8.37 (d, J = 6.7 Hz, 1H), 8.38 (d, J = 6.7 Hz, 1H), 9.17 (s, 1H), 9.19 (s, 1H), 12.80 (s, 1H), 12.96 (s, 1H), 14.91 (br s, 2H) ppm; MS (ion spray): m/z 361 (M+H). $\text{C}_{23}\text{H}_{25}\text{ClN}_4\text{OS}$ MS m/z: 441,443.